REVIEW AND UPDATE OF NONMELANOMA SKIN CANCERS

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CONFLICTS OF INTEREST
- None
- No stock or monetary interests
  (However, we all have our price.)
  (I believe in GOLD: end the FED.)

SKIN CANCERS
- Most common human cancer, half of all cancers.
- Not reported in national cancer registries.
- 50% of Americans develop one by age 65.
- NMSC in 2006 > 1,370,000.
- BCC:SCC 4:1
- 60% of Americans who are fair-skinned develop at least one actinic keratosis by age 40.
- Incidence of SCC has increased 2-3% per year since 1980.
SKIN CANCERS - RISK FACTORS

- Solar exposure, complexion.
- Immunosuppression, immunodeficiencies.
- Ionizing radiation (BCC > SCC).
- Carcinogens.
- Inflammation (local, systemic), oxidative stress.
- Viruses - HPV and others.
- Genetics - detoxifying systems, repair capacity.

VIRUSES AND SKIN CANCER

- Ninety percent of SCCs due to UV exposure.
- HPV clearly associated with SCC cervix, anogenital area, middle finger lesions and in pts with epidermodysplasia verruciformis and probably a role in immunosuppressed pts.
- What about immunocompetent individuals in usual cutaneous sites?

HPV AND SCC

- Case Control Study of 85 immunocompetent pts and 95 immunocompetent controls.
- Highly sensitive PCR detection assays.
- HPV DNA + in 50% of BOTH GROUPS in lesional, perilesional, healthy, sun-exposed and non-sun-exposed skin.
- Conclusion: HPV has high prevalence in humans and role with UV in causing SCC is unclear.

VIRUSES AND NMSC

- PCR for HPV, CMV, HSV and EBV using samples of 26 Aks, 12 SCC and 15 BCCs.
- HPV+ in 8 (31%) of Aks, 15 (33%) of BCCs and 4 (33%) of SCCs.
- CMV+ in 2 (8%) of Aks, 15 (49%) of BCCs and 4 (33%) of SCCs.
- None associated with HSV or EBV.
- Not strong data for these viruses in NMSC.
MERKEL CELL POLYOMA VIRUS

- One of a family of viruses that includes BK virus, JC virus, Simian virus 40, polyoma virus KI and polyoma virus WU.
- MCPyV discovered by digital transcriptome subtraction.
- cDNA from tumor via reverse transcriptase and sequencing the cDNA library.
- All known human sequences are then subtracted leaving nonmatching possibly non-human sequences.
- Clearly associated with Merkel cell Ca; clonally and randomly integrated into genome.

MCPyV and NMSC

- Low detection rate in skin cancers of immunocompetent individuals.
- PCR of Large T Antigen and structural Viral Protein 1.
- Fifty six NMSC from 11 immunosuppressed and 147 NMSC from 125 immunocompetent pts. And 89 normal controls.
- Thirty two percent of sporadic NMSC +
- 37.5% of BCCs + in immunocompetent pts.

LEICHT’S ORIGINAL SIGNS OF SKIN CANCER.

- Any sore that doesn't heal.
- Any amoeboïd lesion on the skin.
- Any jet-black scab on the face, head or neck.
- Any significant scar without a history of trauma.
- Anything red coming off a depigmented area.
- (Any lesion that is persistent, doesn't respond to reasonable therapies and slowly enlarges.)
- (Anything that effaces and alters the underlying texture of the skin).

ACTINIC KERATOSES

- Sandpaper-like, rough red papules on sundamaged skin.
- Sometimes tender-a briar or splinter sensation.
- A precancer that can evolve into a squamous cell carcinoma and rarely into BCC.
- Exact risk?
- Some 25% resolve spontaneously.
ACTINIC KERATOSIS

- Very common in the local adult population.
- Now viewed by many as a focal squamous cell carcinoma.
- Careful sectioning of biopsies show 1/3 have foci of invasive SCC.
- 16% evolve into invasive SCC over 10 years.
- If >10 Aks, 14% risk of SCC in 5 years (2-4% fatal).
- Treatment can be divided between “field therapies” and focal destructive treatments.
- Biopsy any “actinic” that does not resolve with therapy or is very thick or indurated or larger than Actinics should be.
### Focal Treatment of Actinic Keratosis

- **Cryotherapy** with liquid nitrogen or with electronically cooled devices.
- **Curettage and electrodessication**
- **Shave removal.**
- **Bi/trichloroacetic acid.**
- **(Laser)**
- **(Excision)**
- **(Ingenol mebutate)**

### Actinic Keratoses-Treatment

- **Field (regional):**
  - 5-fluorouracil (generic, Fluoroplex, Carac)
  - Imiquimod (Aldara)
  - Diclofenac gel (Solaraze)
  - Photodynamic therapy (Levulan Kerastick, Metvix)
  - Dermabrasion
  - Laser resurfacing
  - Medium depth cutaneous peels

### Basal Cell Carcinoma

- Ironically, not derived from basal cells—probably outer hair root sheath.
- Immunohistochemical markers CK5 and CK14-suprabulbar region of vellus outer hair root sheath.
- May be a result of aberrant follicular organogenesis.
- Hence, only found on hair-bearing skin.
- Doesn’t form significant amounts of keratin-naked shiny tumors.
- Rarely metastasizes, but can be very locally destructive and very occasionally fatal.
- Annual incidence of 0.1-0.5%, 407 per 100,000 males and 212 per 100,000 females.

### BCC Risk Factors

- Tends to be earlier onset than SCC (<50 years old).
- Immunosuppression; Australian heart-transplant pts 21-fold increase and 123x normal Americans.
- As exposure, radiation etc.
- Get one and 10-29 fold increase of a second (i.e. 33-70%) within 3-5 years.
- May be associated with an increased risk of internal malignancy (?).
**BCC RISK FACTORS**

- Recreational sun exposure early in life.
- Intense intermittent exposure > continuous exposure.
- Fair complexion, light hair, multiple nevi, easily burned.
- Inverse relationship with wrinkling.
- Rare on dorsal hand, uncommon on arm, relatively common on the trunk.
- Even on face not correlated strictly to sun exposure.
- BCC:SCC 3-4:1

**RISK FACTOR-TRAUMA**

- May arise in sites of acute or chronic trauma:
  - Vaccination sites
  - Venipuncture injuries
  - Leg ulcers-venous and others
  - Cryosurgery sites?

**SITES OF BCC**

- Usually “T” area of face, head and neck (80%).
- Development of truncal lesion (15%) portends high risk of multiple tumors over time.
- Relatively rarer on dorsal hands, extremities and scalp.
- Rare sites-genitals, perirectal, periungual, areola, junctional palmar and plantar skin

**CLINICAL FEATURES OF BCC**

- Pinkish gray and translucent (rose quartz), NOT USUALLY PEARLY.
- Waxy, milky.
- Rolled margins (pushing borders)
- Telangictasia (neovascularity).
- Minimal to no scale, horns or hyperkeratosis.
BCC SUBTYPES
- Nodular.
- Superficial.
- Pigmented.
- Morpheaform/sclerosing.
- Ulcerative.

LEICHT'S ORIGINAL, NEVER COPIED

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MOLECULAR PATHOGENESIS

- Hedgehog family intercellular signaling pathway activation occurs.
- Highly conserved regulator of cell growth during embryogenesis and controls aspects of epithelial and mesenchymal interaction, inactive in most adult tissues.
- Sonic HH = patched homologue 1 (PTCH1) = G-protein coupled receptor smoothened (SMO).
- PTCH gene is on chromosome 9q (9q22.3).
- Hedgehog signaling mutations in 30-40% of sporadic BCCs; also in medulloblastoma and rhabdomyosarcoma.
- P53 tumor-suppressor mutation (UV signature) in 50%.
**MOLECULAR PATHOGENESIS**

- Stratified squamous epithelium expressing SHH fails to exit S and G2/M phases of mitosis.
- Even in sporadic BCCs without PTCH 1 mutations, almost all show overexpression of PTCH 1 mRNA cytoplasm via RT-PCR.
- PTCH 1 protein accumulation detected in cytoplasm of ALL sporadic BCCs.
- Heaviest concentrations PTCH 1 in proliferating/invasing outer palisading layer of tumor cells.
- Continued SHH signaling maybe necessary for survival and growth of BCC.
- Transgenic mouse models indicate HH signaling mutation is sufficient to cause BCC without UV etc.

**HIGH RISK BCC RECURRENCE, METASTASIS**

- Size > 2.0 cm.
- Central face and ears.
- Long duration.
- Aggressive histology; micronodular, infiltrative, basosquamous, morpheaform and mixed.
- Perineural, perivascular spread.
- Recurrence after treatment.

**SKIN CANCER TREATMENTS**

- Curettage and electrodessication.
- Simple excision
- Excision with grafts, flaps or second intention healing.
- Cryosurgery
- Moh's surgery
- Radiation therapy

**BCC**

- Metastatic rate of .0028%-0.55%.
- Usually large tumors of more than 9 years duration.
- Spreads to lymph nodes (70%) , lung, skin and bone.
- Median survival 8 mos.
**TREATMENT OF BCC BY INHIBITION OF HEDGEHOG PATHWAY**

- Phase I trial of 33 patients with locally advanced or metastatic BCC.
- Eighteen (55%) metastatic and 15 (45%) locally advanced.
- Therapy with GDC-0449 which binds to SMO and inhibits downstream hedgehog target genes.
- Locally advanced disease: 2 complete response, 7 partial and 4 stable.
- Metastatic: 9 partial responses and 7 stable disease.


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**SQUAMOUS CELL CARCINOMA**

- Second most common skin cancer (1st if you accept Ak).
- Found wherever stratified squamous epithelia found.
- Derived from basal cells-unlike basal cell carcinoma (!).
- Polyclonal malignancy (field cancerization).
- Programmed to produce keratin and scale.
- Can metastasize depending on site and circumstance.
- Precursor lesion on skin is the actinic keratosis.

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**SQUAMOUS CELL CARCINOMA**

- Less diagnostic clinical appearance.
- Reddish milky-white OPAQUE tumor.
- Usually produces irregular keratin and scaling.
- Dome shaped, irregular or volcano shaped, opaque, indurated mass with central or irregular keratin plug.
- Mass underlying cutaneous horn.
- Amoeboid scaley irregular plaque.
- Irregular white or red patches on mucosa.
- Ulcerations.

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**SQUAMOUS CELL CARCINOMA SUBTYPES**

- SCC in-situ ; Bowen’s disease, erythroplasia of Queyrat, “red leukoplakia”.
- Keratoacanthoma.
- Nodular.
- Ulcerative
- At scar sites e.g. Marjolin’s ulcer.
- Verrucous carcinoma
KERATOACANTHOMA

- Very rapid growth to a bulging tumor with a central keratin core.
- May grow over 4-8 weeks to a golf-ball size.
- Histology is of a well-differentiated SCC.
- If untreated (!) *USUALLY* involutes slowly to an irregular, ragged scar.
- Most researchers and almost all clinicians regard it as a variant SCC.

SCC-NATURAL HISTORY

- Six hundred and fifteen pts followed for up to 15 years.
- All were invasive lesions.
- Two-10mm margins removed surgically.
- Twenty (3%) locally recurred.
- Twenty six (4%) developed mets.
- Most mets were at diagnosis or within first year, none after 4 years.
- No tumor < 4mm thick metastasized.

**FOLLOW-UP**

- Five year rate of recurrence is 8%, 5 year rate of mets is 4-5%.
- About 58% of recurrences and metastases within one year and 75-80% within first 2 years.
- Surveillance for new NMSC - within 4 years 30%-60% have second lesion, one half in first year.


**HIGH RISK SCC**

- Location: ears, central face, parotid area, mucosa, ulcers, radiation damage etc.
- Rapid growth, size >2cm.
- Depth into reticular dermis or subQ (>4mm: recurrent, >10 mm: potentially fatal).
- Immunosuppression.
- Perineural spread.
- Histology: poorly diff, desmoplastic, spindle cell.
- Recurrent tumors; >25% eventually metastasize.

**MUCOSAL SCC**

- Except for thinnest lesions on mucosa, standard of care in US is to do prophylactic neck dissection.
- Even with negative clinical neck exam, 33% will have micrometastatic nodal disease with 33% extracapsular at diagnosis.
- However, lymph node drainage for head and neck is complex and unpredictable.
- In Europe Sentinel Lymph Node Biopsy (SLNB) is commonly utilized.
- SLNB technique for SCC complicated by false negatives.

**HIGH RISK SCC-APPROACH**

- Larger than standard margin - probably not!
- Sentinel node biopsy?
- Imaging studies; MRI, CT, PET?
- Prophylactic radiation therapy?
- Acetretin?
- No data that detection and treatment of lymph node disease actually improves survival.
NMSC IN TRANSPLANT RECIPIENTS
- Up to 70% may develop NMSC; most (~90%) are BCCs and SCCs.
- More SCCs than BCCs (2.6:1).
- SCC is 65-250 times more common in OTRs.
- BCC is 10 times more common.
- Risk of BCC is linear over time; risk of SCC is exponential.
- Frequently an accelerating pattern of SCCs.
- Kaposi’s sarcoma is increased 84 fold.
- Other cutaneous malignancies are variably increased.

SKIN CANCER AND TRANSPLANTATION
- By 10 years s/p organ transplant up to 43% incidence of NMSC.
- Cumulative incidence parallels survival.
- Older age correlates with shortened latency to first NMSC.
- Incidence reflects intensity and duration of immunosuppression.
- Location of tumors highly biased to sun-exposed areas.
- Risk is augmented by past and concurrent UV exposure.
- High association with concurrent HPV infection (potpourri of HPV subtypes).

NMSC AND TRANSPLANTATION
- Risk correlates with intensity of immunosuppression (cardiac transplants 3X incidence and develop sooner than renal transplants).
- Rate of cancers (and warts) decelerates within 1-2 years when immunosuppressives are discontinued.
- Azathioprine (a mutagen) in high cumulative doses has nearly 9 fold increased risk of SCC compared to patients not treated with azathioprine.
- Cyclosporine (a carcinogen) has 8 fold increase in NMSC after adjustment for risk factors.

NMSC AND IMMUNOSUPPRESSION
- More aggressive behavior.
- Local recurrences in 13.4% of patients usually in first 6 months.
- 5-8% metastatic rate by 2 years.
- 50-60% survival rate for metastatic disease.
- Lethal skin cancers account for about 25% of post-transplant deaths in series.
- In cardiac transplants 41% developed skin cancer within 2 years and 50% died.
SKIN CANCER AND TRANSPLANTATION-PREVENTION

- Photoprotection and sun avoidance (poor compliance).
- Limiting intensity of immunosuppression.
- Avoiding azathioprine and cyclosporine.
- Systemic retinoids: acetretin.

PREVENTION

- Less intense immunosuppressive regimens.
- Sirolimus has an antineoplastic action-substitute for azathioprine and cyclosporine.
- Retinoids bind and activate PPAR-gamma.
- Increases differentiation, inhibits proliferation, increases apoptosis.
- Destruction of Aks with cryotherapy, 5-flurouracil, imiquimod, resurfacing procedures?

RETINOIDS IN CHEMOPREVENTION

- Demonstrated efficacy in decreasing new SCCs (and BCCs) in RCTs.
- Effective in decreasing SCC and BCC in pts with xeroderma pigmentosum.
- 72% reduction in one study of renal transplants over 5 years.
- 80% reduction in NMS for 10-24 mos c/w pretreatment period.
- Crossover prospective study showed 42% reduction in new NMSC on acitretin treatment.

RETINOID CHEMOPREVENTION

- Acetretin, Isotretin

- More than 5-10 SCCs in a year (even one?).
- Accelerating pattern of NMSCs.
- Innumerable Aks in association with SCCs.
- High risk lesions.
- Metastatic disease
- However, may lose some efficacy after 3-5 years.
- Issues of morbidity and tolerance.
- Goal is reduction, not elimination of risk.
“I predict future happiness for Americans if they can prevent the Government from wasting the labors of the people under the pretense of taking care of them.”

“If the American people ever allow private banks to control the issue of their currency, first by inflation, then by deflation, the banks and corporations that grow up around the banks will deprive the people of all their property until their children wake up homeless on the continent their fathers conquered.”

“The democracy will cease to exist when you take away from those who are willing to work and give to those who would not.”

Thomas Jefferson

WAKE UP AND SMELL THE TEA!

QUESTIONS?
PHOTOAGING AND PHOTODAMAGE

- Wrinkling
- Elastosis
- Atrophy
- Telangiectasia and ruddy complexion
- Bruising, solar (senile) purpura
- Nuchae rhomboidalis
- Poikiloderma of Civatte
- Sagginess, sallowness, porosity etc.