Identifying and Treating Skin Cancer and Cutaneous Toxicities of Immunosuppressive Medications in Solid-Organ Transplant Recipients

Frank Santoro, MD FAAD
Medical Director of Dermatology at Hartford HealthCare Medical Group
Clinical Instructor, Yale University Department of Dermatology
Clinical Assistant Professor, Quinnipiac School of Medicine
frank.santoro@hhchealth.org
Learning objectives for today

- Identify risk factors for the development of cutaneous malignancies in solid-organ transplant recipients and take proactive approaches to decrease their risk of skin cancer.

- Develop a comprehensive approach to skin cancer and start to build an infrastructure for skin care prior, during and after transplantation.

- Recognize cutaneous toxicities from commonly used treatments for solid-organ transplant recipients and understand potential treatment options.
Why care about skin cancer in solid organ transplant recipients (SOTR)?

- Skin cancer is the most frequent malignancy post-transplantation.
  - 10 times the risk for basal cell carcinoma (BCC)
  - 65 times the risk for squamous cell carcinoma (SCC)
    - Most common type of skin cancer in SOTR
  - Account for about 5% of skin malignancies
    - Melanoma (3x greater risk than general population)
    - Higher risk for Merkel cell carcinoma and Kaposi’s sarcoma
SCC development causes greater morbidity and mortality

- The risk of SCC development in the US post-transplant:
  - 10 years: 10-27%
  - 20 years: 40-60%.
- The risk of metastasis of SCC in SOTR is 8%, whereas general population it’s 0.5-5%.
- Cincinnati tumor registry: 5.2% of SOTRs died from a skin malignancy
  - SCC was 62% of these deaths
- Rate of SCC decreases if develop sun-protective measures.
Immunosuppression promotes skin cancer development

- Heart and lung transplant recipients have a greater risk of skin cancer since higher amount of immunosuppression and usually older age at time of transplant.
- Retrospective study of 166 lung transplant recipients at Mayo Clinic
  - 5, 10 year cumulative incidence (%, %)
    - 31%, 47% for any skin cancer
    - 28%, 42% for SCC
      - Incidence of second SCC after first SCC was 80% over 4 years
    - 12%, 21% for BCC
- Compared to heart transplant recipients, lung transplant patients had more morbidity from metastatic SCC
What is the role of immunosuppression in cancer promotion?

1) inhibition of immune reactions capable of recognizing and destroying tumor cell

2) the permissiveness of viral infections that are associated with common skin cancers
   - Human papilloma virus (HPV): SCC
   - Human herpes virus-8 (HHV): Kaposi’s sarcoma
   - Merkel cell polyomavirus: Merkel cell carcinoma

3) Direct effect of immunosuppressive agents
   - Cyclosporine: promotes tumor cell invasiveness, increases angiogenesis, inhibits DNA repair
   - Azathioprine: Mutagenic effect that synergizes with UV radiation
History of skin cancer prior to transplantation might be associated with poorer posttransplant outcomes

- Retrospective study of primary adult kidney recipients 2005-2013. 1671 recipients with and 102,961 without pretransplant skin malignancy.
  - 5 year cumulative incidence of posttransplant malignancy was 31.6% and 7.4%, respectively.
  - Recipients with pretransplant skin cancer had increased risk of:
    - Posttransplant malignancy (sub-HR(SHR), 2.6 (2.27-2.98))
    - Posttransplant skin cancer (SHR, 2.92 (2.52-3.39))
    - Posttransplant lymphoproliferative disorder (SHR, 1.93 (1.01-3.66))
    - Solid tumor (SHR, 1.44 (1.04-1.99))
    - Death (Hazard Ratio (HR), 1.20 (1.07-1.34))
    - Graft failure (HR, 1.17 (1.05-1.30))
What can be done to reduce the morbidity and mortality of skin cancer in SOTR?

Recognition
When you see a lesion, ask yourself: Benign or malignant?

**Benign**
- Well-circumscribed
- One color
- No ulceration
- If a nodule, mobile
- Small
- Similar growths on body

**Malignant**
- Ill-defined margins
- Multiple colors
- Ulceration
- Pain
- Irregular
- No other similar growths
Recognition of squamous cell carcinomas
Squamous cell carcinoma

Associated risk factors: smoking, age, alcohol consumption, exposure to sunlight
SCC histology

• Pain is the most consistent sign of invasiveness of SCC
• High risk areas
  – Eyelids, lips, ears, penis
• SCC have a higher risk of recurrence
• On histology, SCC in SOTR tend to be:
  – have greater tumor depth
  – greater incidence of perineural or lymphatic invasion
Leukoplakia (pre-cancerous) areas
Actinic chelitis (pre-skin cancerous changes of the lips)
Squamous cell carcinoma
Squamous cell carcinoma in-situ
Basal cell carcinoma - shiny, telangiectasias
Basal cell carcinoma
-rolled border
-ulceration
Merkel cell carcinoma

- Red nodule
- Friable
- Sun-exposed area
- Rapid growth (months)
- High chance of regional metastasis
Merkel Cell Carcinoma
Kaposi’s sarcoma
-red patches or nodules
Kaposi’s sarcoma (patch stage)
Kaposi’s sarcoma (palpable lesions)
Kaposi’s sarcoma (palpable lesions)
How to examine for pigmented suspicious lesions: “ugly duckling sign”

Figure 1. Three Examples of an Ugly Duckling
Detection acronym: ABCDE

- **A** ssymetry
- **B** order
- **C** olor
- **D** iameter
- **E** volving
Different types of melanoma

- Superficial spreading melanoma
- Nodular melanoma
- Lentigo maligna
- Acral lentiginous melanoma
Melanoma
Dermoscopy helps to identify melanoma through recognition of patterns.
Nodular Melanoma
- breaks ABCDE rules
- very fast growing (months)
Melanoma of the nail unit

• Higher suspicion if:
  – Nail destruction
  – Involvement of the nailfold
  – Greater than 3mm wide

• Can have persistent dark bands in nails from:
  – Normal skin variant (esp darker skin)
  – Nevus of the nail
  – Medications
Melanoma of the nail unit
Amelanotic melanomas
-not all melanomas are black
Melanoma and SOTR

• The mean duration posttransplant to development of melanoma is 5 years.
• Seen more likely on the head and neck.
  – Melanomas in non-transplant
    • Men more likely on back
    • Women more likely on lower extremities
• SOTRs tend to have more regional disease.
• SOTRs have a 3x higher risk of dying from melanoma (even melanomas less than 1mm).
Important determinants for cutaneous malignant melanoma risk

- Personal and family histories (1st degree relative) of malignant melanoma
  - Survivors of melanoma are about nine times as likely as the general population to develop a new melanoma.
- Presence of atypical nevi
- Large numbers of nevi (over 100)
- History of indoor tanning
  - More than 419,000 cases of skin cancer in the US each year are linked to indoor tanning, including about 245,000 basal cell carcinomas, 168,000 squamous cell carcinomas, and 6,200 melanomas.
  - More people develop skin cancer because of tanning than develop lung cancer because of smoking.
- History of sunburn
  - About 86 percent of melanomas can be attributed to exposure to ultraviolet (UV) radiation from the sun.
  - On average, a person’s risk for melanoma doubles if he or she has had more than five sunburns.
- Fair skin types
- Certain conditions
  - genetic susceptibility
  - genetic albinism diseases
  - medium-large congenital nevus—greater than 5 cm
  - Prior history of lymphoma
What do we know about patients and self-detection?

- Women more likely than men to undergo self-examinations.
- Younger more likely to detect melanomas than older.
- Gender differences in detection:
  - Women: recognize color variation more often
  - Men: recognize irregular borders more often. Their partners often find the melanomas.
- 3,772 residents in Queensland Australia where melanoma confirmed
  - 44%: detected by patients
  - 25.3%: physicians
  - 18.6%: partners
What is the best way to biopsy skin cancers?
Shave biopsies

- Best for superficial lesions
  - BCC, SCC
- With experience, can use for melanocytic lesions (lesions suspicious for melanoma)
  - Risk: Can miss the deepest portion of a melanoma
    - Depth of melanoma changes prognosis
    - Depth of melanoma determines treatment (sentinel lymph node biopsy, staging studies)
Punch biopsy

My main use:
- Rashes
- Small melanocytic tumor
  - Can excise the lesion with a punch biopsy
  - If only take samples of melanocytic tumor, might miss true depth
  - Pathologists prefer full architecture of melanoma when making diagnosis
Excisional biopsy

- I remove melanocytic tumors suspected of melanoma with 2mm margins down to the superficial fat
- I let the pathology lab know that I excised the tumor (they section the specimen differently and allow for margin control)
- If you are really worried about a tumor and path report benign, don’t be afraid to get a second opinion
  - Best if a dermatopathologist reads the slide
What should be done prior to transplant?

- Does the patient have a history of pre-transplant skin malignancy?
- Identify risk factors for the development of skin cancer
- Counsel patients about sun-protective methods
If a transplant candidate had skin cancer, how long should patient wait prior to transplant?

- **SCC history**
  - Uncomplicated: proceed to transplant
  - High risk SCC: Wait 2 years prior to transplant with no mets on CT or PET-CT
  - If high risk SCC with perineural invasion: Wait 3 years prior to transplant with no mets on CT or PET-CT
  - If SCC with nodal involvement, then wait 5 years prior to transplant

Zwald, 2016
If a transplant candidate had skin cancer, how long should patient wait prior to transplant?

**Melanoma**
- Melanoma in-situ history: proceed to transplant
- Stage Ia: Wait 2 years prior to transplant
- Stage Ib/IIa: Wait 2-5 years prior to transplant
- Stage IIb/IIc: Wait 5 years prior to transplant

**Merkel cell carcinoma**
- Local with negative SLN: Wait 2 years prior to transplant
- Local with nodal metastasis: Wait 3-5 years prior to transplant
- Distant metastasis: Ineligible for transplant

Zwald, 2016
What are the risk factors for skin cancer development in SOTRs?

- Fitzpatrick skin type I to III
  - Ranging from always burn & no-tan to burn & then tan
- Longer duration and higher level of immunosuppression
- Increasing age at the time of transplantation
- Type of organ transplant (Lung > heart > kidney > liver)
- Previous organ transplant
- History of lymphoma
- Squamous cell carcinoma before transplant
- Extensive sun damage (actinic keratoses)
Extensive actinic keratoses
How should patients be counseled?

• Should counsel patients prior and after transplant on sun-protective behaviors.
  – Broad-spectrum sunscreens
    • SPF 30 sunscreen (UVA/UVB) protection 15 minutes prior to going outside and re-apply every 2 hours
  – Avoid outdoor activities from 10am-4pm
  – Self skin examinations every 2-3 months with lymph node palpation in high-risk individuals
  – Wear sun-protective clothing, lip balm with sunscreen as well as long-sleeves, wide-brimmed hats and sunglasses
  – Refrain from indoor tanning

• Check Vitamin D levels posttransplant and supplement if necessary
What should be done in the posttransplant period?

- Risk-stratify patients to undergo skin cancer screening
- Be proactive with sun damaged skin
- Treat skin cancers early
- Be proactive with patients developing many squamous cell carcinomas
### Risk-stratification of when to have patients undergo skin cancer screenings

<table>
<thead>
<tr>
<th>Questions asked to assess risk</th>
<th>Points for “yes” responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever had a skin cancer?</td>
<td>5</td>
</tr>
<tr>
<td>Are you outside for more than one hour per day?</td>
<td>2</td>
</tr>
<tr>
<td>Are you older than 50 years of age?</td>
<td>2</td>
</tr>
<tr>
<td>Have you lived in a hot climate for more than 30 years?</td>
<td>2</td>
</tr>
<tr>
<td>Have you ever experienced sunburn as a child or a teen?</td>
<td>1</td>
</tr>
<tr>
<td>Is your skin tone light or very fair in color? (Fitzpatrick skin phenotype I)</td>
<td>1</td>
</tr>
</tbody>
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**Points**

- 7 and greater: First post-transplant screening
- 5-6: 6 months
- 4 and below: 2 years
- 5 years
Are there any proactive measures that can be taken for transplant patient with a lot of sun damage?

- **Use of topical creams**
  - If reduced damage, might be less prone to developing skin cancers
  - 5-fluorouracil (Efudex, Carac)
  - Imiquimod (Aldara, Zyclara)
  - Ingenol mebutate (Picato)

- **Photodynamic therapy**
  - Placement of sensitizing agent (aminolevulinic acid) followed by blue/red light therapy to decrease number of actinic keratoses

- **Unclear benefit**
  - Nicotinamide (Vitamin B3), might be anti-inflammatory, in doses of 500 mg PO BID
    - Hasn’t been studied in SOTR
    - Side effects minimal
    - OTC
Once these skin cancers are identified, how are they treated?
Mohs surgery for BCC and SCC

- Standard of care for SCCs with ill-defined margins, in high-risk locations (ears, lips, eyelids, face), perineural invasion, greater than 2 cm
What if patients continue to develop skin cancers?
What if patients posttransplant develop many squamous cell carcinomas?

• Many SCC defined by 5-10 SCC a year

• Options
  – Decrease/change amount of immunosuppression
  – Initiate an oral retinoid
  – Switch to mTOR inhibitor (sirolimus/everolimus)
    • controversial
Acitretin decreases incidence of SCC

- Acitretin, an oral retinoid, decreases the rate of SCC development in high risk individuals
- Potential side effects
  - Mucocutaneous dryness, hair loss, musculoskeletal pain
  - Increased triglycerides and increased cholesterol
    - Need to monitor LFTs, CBC, fasting lipids monthly during dose escalation and then every three months
  - Teratogenicity
    - Should not be given to individuals who want to have children
    - Can potentially last in the body for 3 years after use
- Starting dose
  - 10 mg every other day and increased as tolerated to 25-30 mg per day.
- Once medication stopped, incidence of SCC returns to individual’s baseline
  - It suppresses SCC, but doesn’t cure them
mTOR inhibitors might have an antitumoral effect

- Reasoning for possible protective effect against skin cancer
  - mTOR inhibition promotes T regulatory cell development.
  - mTOR pathway is important for angiogenesis and skin tumors depend on angiogenesis. If inhibited, then no angiogenesis and less skin tumors.
  - mTOR inhibitors have an antiviral effect
The data for mTOR inhibitors (sirolimus, everolimus) decreasing rate of skin cancer is controversial

- **NEJM study**
  - In a study of 53 renal transplant patients who developed skin cancer, there was regression of NMSC in 37 patients.

- **Since then, mixed reports**
  - An RCT showed an initial reduction in SCC development, but insignificant after 2 years
  - Kaiser Permanente study from 2000-2010 with 3539 SOTR, of whom 488 had sirolimus. Showed no reduction in posttransplant SCC risk

- **What’s agreed on for sure:**
  - Should only be used in patients with 6 months of stable grafts
  - Best results on patients with single, not multiple SCC

*Geissler, 2015
Asgari, 2015*
Cutaneous side effects of medications used in patients with solid organ transplants
Prednisone: Hair loss

First-line treatment:
- minoxidil 5% foam daily (takes at least three months to work)
  - chronic treatment
  - side effects: irritation, initial shedding, distant hair growth
Prednisone: Hirsuitism

Treatments
- Depilatory agents (OTC)
  Side effect: irritation
- Laser hair removal
- Eflornithine (Vaniqa) cream
  - chronic treatment, decrease rate of hair growth
Prednisone: Acne/folliculitis

Treatments

- Benzoyl peroxide 5% wash daily to face; 10% to trunk (OTC)
- Clindamycin lotion or benzoyl peroxide 5%-clindamycin 1% combo gel
- Doxycycline 100 mg PO daily x 2 months with topical therapies above
Cyclosporine: Gingival hyperplasia
Cyclosporine: Sebaceous hyperplasia
Sulfamethoxazole/trimethoprim: Morbilliform drug rash
Sulfamethoxazole/trimethoprim: Stevens-Johnson Syndrome/Toxic Epidermal Nerclysis
Sulfamethoxazole/trimethoprim: Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

• Criteria
  – 2 mucosal surface
  – Medication exposure: 1-3 weeks (usually less than two)
  – Widespread erythematous morbilliform rash with blistering

• Definitions
  – SJS: less than 10% BSA
  – TEN: Greater than 30% BSA
Voriconazole: photosensitivity

Might also induce SCC and melanoma formation

Note: azathioprine can also cause photosensivity
Mycophenolate mofetil: Aphthous ulcerations

Appear 1 week to 3 years after starting mycophenolate
Questions/comments?

Frank Santoro, MD
frank.santoro@hhchealth.org
Bibliography

- Geissler EK. Skin cancer in solid organ transplant recipients: are mTOR inhibitors a game changer? Transplant Res. 2015 Jan 14;1:1