Erika Tvedten, PGY-2
Dermatology Journal Club
August 2023

JAMA: APOA4 as a novel predictor of prognosis in Stevens-Johnson syndrome/toxic epidermal necrolysis: A proteomics analysis from two prospective cohorts

- *What is the general condition, procedure or disease under study?*
  - Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening adverse drug reactions characterized by epidermal detachment and mucosal erosions. Although many research endeavors, the molecular mechanism of SJS/TEN is still not fully understood, and there is no ‘‘gold standard’’ for their treatment.
- *What were the research question(s)?*
  - Is it efficacious and safe to use the combination treatment with a tumor necrosis factor-alpha antagonist adalimumab and corticosteroids?
  - Does APOA4 serve as an indicator of clinical prognosis?
- *Was the question answered to your satisfaction - validity? Do you trust the conclusions and recommendations?*
  - There were two cohorts of patients in this retrospective study, one cohort with 48 patients (57.83%) receiving methylprednisolone monotherapy (with an initial dose in the range of 1 to 1.5 mg/kg/day) and one cohort with 35 patients (42.16%) receiving the combination therapy with additional adalimumab (80 mg in a single subcutaneous injection).
    - The primary outcome parameter was the time to re-epithelization while the secondary outcome parameters included the time for skin and mucous healing, the time to complete pain relief, the tapering course of methylprednisolone, and the total dosage of methylprednisolone (mg/kg). The median time to reepithelization was 8.0 days (IQR: 7.0-9.8) for those treated with methylprednisolone and 7.0 days (IQR: 5.0-9.0) for those treated with combination therapy.
  - Based on the results, addition of etanercept to the steroid treatment could reduce the time of skin healing by one day as well as safety of adverse drug effects compared to steroids alone. This would then direct the question to is the day of faster healing worth the extra money for the biological combination therapy.
  - The level of APOA4 was found to be positively correlated with a decline in TNF-a levels ($r = 0.797$, $P < .0001$).
    - APOA4 has potential to be a marker of disease progression in SJS/TEN because circulating APOA4 level was negatively correlated with TNF-alpha expression in SJS/TEN patients and a similar phenomenon was seen in cohort 1, where the levels of APOA4 increased after steroid monotherapy.

    - I trust that this a hopeful avenue to explore for treatment management of SJS/TEN and could possibly be considered in clinical practice for monitoring disease progression in the future, however, with the low sample size and wide IQR, I don't think we should be making this a set protocol but rather used for the right patient. More studies are needed.
- *Does this study prompt or inspire a different and better study?*
    - This a smaller sample size (total of 83 patients separated into two cohorts) larger studies and multicenter locations would be an ideal next step in investigation.
    - When dealing with the current severity of illness score for toxic epidermal necrolysis, there is no significant association with APOA4 and further investigation into this specific question will be needed.

JAMA: Validation of the 2022 National Comprehensive Cancer Network Risk Stratification for Cutaneous Squamous Cell Carcinoma

- *What is the general condition, procedure or disease under study?*
    - The second most common keratinocyte carcinoma is Cutaneous squamous cell carcinoma and is typically managed with Mohs or wide local excision. However, few patients go on to develop poor outcomes, including local recurrence, nodal metastasis, distant metastasis and disease-specific death.
    - The current staging systems are the American Joint Committee on Cancer's cancer staging manual and the Brigham and Women's hospital staging system that are based on tumor characteristics that have been shown to impact prognosis such as tumor diameter, poorly differentiated histologic findings, perineural invasion of large tumor diameter, poorly differentiated histologic findings, perineural invasion of large-caliber nerves, and deep tumor invasion.
    - While useful for prognostication, current staging systems do not incorporate patients' factors or other high-risk tumor features that influence outcomes.
- *What were the research question(s)?*
    - What are the outcomes of very high-risk, high-risk, and low-risk National Comprehensive Cancer Network groups of cutaneous squamous cell carcinoma?
    - What are the comparisons between the treatment with Mohs or peripheral and deep en face margin assessment compared with wide local excision for cutaneous squamous cell carcinoma?
- *Was the question answered to your satisfaction - validity? Do you trust the conclusions and recommendations?*
    - This retrospective cohort study was a large study across two institutions (Cleveland clinic and Brigham and women's) of 8727 patients with a total of 10196 cutaneous squamous cell cancers put into groups of low-risk, high risk, and very high risk.
    - Patients who fall into high and very high-risk groups have a significantly higher increased risk of developing local recurrence (, nodal metastasis, distant metastasis and of dying from their disease.

    - Mohs or PDEMA had a 35% lower risk of local recurrence (95% CI, 0.46-0.90; *P* = .009), nearly 60% lower risk of distant metastasis (95% CI, 0.18-0.83; *P* = .02), and a 45% lower risk of DSD (95% CI, 0.36-0.84; *P* = .006) compared with wide local excision.
    - I think this is a strong study that suggests the new NCCN guidelines is a unique tool (compared to what is already available with the AJCC-9 and BWH) that will allow for risk stratification in a clinical setting allowing clinicians to incorporate the patient's clinical appearance in addition to pathological findings.
    - Mohs and PDEMA provide the least risk of local recurrence, nodal metastasis or distant metastasis and disease specific death and should be considered over wide local excision.
- *Does this study prompt or inspire a different and better study?*
    - As this is a retrospective study, one should be weary of underreporting of certain risk factors as they are not readily available.
    - When considering further studies, it would be helpful to initiate a side-by-side comparison of all three tools for risk stratification in a prospective study.
    - It still remains unclear if high-risk tumors benefit from closer surveillance and additional therapies.

TRANSPLANTATION DERMATOLOGY: RACE MATTERS

By Warren R. Heymann, MD, FAAD
June 21, 2017

December 3rd, 2017 will mark the 50th anniversary of the first human-to-human heart transplant performed by the late South African cardiothoracic surgeon, Christaan Barnard. On Dec. 2, 1967 Denise Darvall, a 25-year old accounting-machine operator, was struck by an automobile while crossing a street in Cape Town. She was found to be clinically brain dead but her heart was in good condition. She had the same blood type as Louis Washkansky, a grocer, who became the first cardiac transplant recipient. He died 18 days later of pneumonia attributed to immunosuppression from azathioprine and steroids (1).

Half a century of progress in transplantation has fostered tremendous progress — mortality following solid organ transplantation is decreasing due to improved immunosuppressant regimens and better surgical outcomes. Currently, there are

170,000 solid organ recipients in the USA. As transplanted patients live longer, their level of risk for acquiring malignancies, especially skin cancers, increases. More than 50% of solid organ recipients will be diagnosed with at least one skin cancer. There is also increased risk for squamous cell carcinoma (SCC) of 65–250 times and for basal cell carcinoma (BCC) of 10–16 times those of the general population (2). Although chronic graft rejection remains a leading cause of post-transplant mortality, death due to malignancy in organ transplant recipients (OTR) may occur in up to 12% of subjects in the United States, with nonmelanoma skin cancer (NMSC) being the most common. This is especially true for older, white, male patients who are thoracic transplant recipients (3).

What is the risk of NMSC in OTR patients of color?

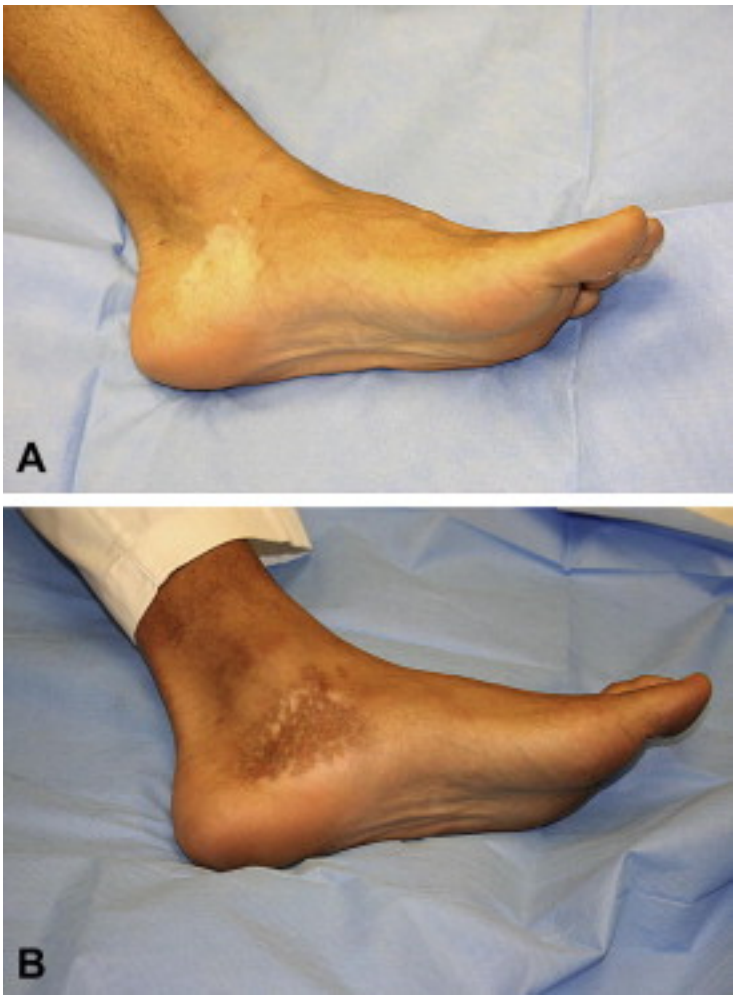
Chung et al performed a retrospective review of 412 OTRs treated at Drexel University's multidisciplinary transplantation clinic. Prevalence and characteristics of cutaneous disease were compared in 154 white and 258 nonwhite (Asian, Hispanic, and black) OTRs.

The 412 patients undergoing analysis included 264 men (64.1%) and 148 women (35.9%), with a mean age of 60.1 years. White OTRs more commonly had malignant disease at their first visit (82 [67.8%]), whereas nonwhite OTRs presented more commonly with infectious (63 [37.5%]) and inflammatory (82 [48.8%]) conditions [See the appendix below for a list of these disorders]. Skin cancer was diagnosed in 64 (41.6%) white OTRs and 15 (5.8%) nonwhite OTRs. Most lesions in white (294 of 370 [79.5%]) and Asian (5 of 6 [83.3%]) OTRs occurred in sun-exposed areas. Among black OTRs, 6 of 9 lesions (66.7%) occurred in sun-protected areas, specifically the genitals. Fewer nonwhite than white OTRs reported having regular dermatologic examinations (5 [11.4%] versus 8 [36.4%]) and knowing the signs of skin cancer (11 [25.0%] versus 10 [45.4%]).

The authors concluded that treatment of nonwhite OTRs should focus on inflammatory and infectious diseases. Sun protection should continue to be emphasized in white, Asian, and Hispanic OTRs. Black OTRs should be counseled to recognize the signs of genital human papillomavirus infection. Optimal posttransplant dermatologic care may be determined based on the race or ethnicity of the patients, but a baseline full-skin assessment should be performed in all patients. All nonwhite OTRs should be counseled more effectively on the signs of skin cancer, with focused discussion points contingent on skin type and race or ethnicity (4).

Regardless of race, long-term immunosuppression in organ transplant recipients (OTRs) leads to decreased immune-mediated tumor surveillance and development of malignancies. A delicate balance needs to be maintained in the intensity of immunosuppression to keep the risk of malignancy low without jeopardizing life-saving graft function. In addition to SCCs and BCCs, other reported skin cancers in OTRs include Kaposi's sarcoma, Merkel cell carcinoma and malignant melanoma. Tumors in this high-risk population are aggressive and may respond poorly to standard therapies. Fortunately, new, targeted therapies are promising. Checkpoint inhibitor antibodies have been used for treatment of cutaneous SCC, Merkel cell carcinoma, and MM; epidermal growth factor receptor inhibitors for cutaneous SCC; hedgehog pathway inhibitors for BCC; and BRAF and MEK inhibitors are being used increasingly in the management of MM in OTRs. (5)

Vigilance in screening for skin cancer, sun protection, consideration for use of the HPV vaccine, and administration of retinoids (notably acetretin) are vital in preventing skin cancers in this high-risk group. Other chemoprevention therapies currently being studied include difluoromethylornithine, cyclooxygenase inhibitors, nicotinamide, and antioxidants.(2). Christina Chung and her group have offered a refined pathway for skin cancer prevention in our increasingly multicultural society. This should help reduce morbidity and mortality in transplant patients of all races and ethnic backgrounds.



1. Altman LK. Christiaan Barnard, 78, Surgeon for first heart transplant, dies. New York Times, Sept 3, 2001.
2. Perez HC, et al. Basic aspects of the pathogenesis and prevention of non-melanoma skin cancer in solid organ transplant recipients: A review. Int J Dermatol 2017; 56: 370-8.
3. Garrett GL, et al. Trends of skin cancer mortality after transplantation in the United States: 1987 to 2013. J Am Acad Dermatol 2016; 75: 106-12.
4. Chung CL, et al. Comparison of posttransplant dermatologic diseases by race. Arch Dermatol 2017; 153:552-8.
5. Mittal A, Colegio OR. Skin cancers in organ transplant recipients. Am J Transplant 2017. May 29 [Epub ahead of print]