Beyond *JAAD* January 2019: Articles of interest to dermatologists from the nondermatologic literature

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COMPLETE RESPONSE OF EXTRAMAMMARY PAGET'S DISEASE WITH IMIQUIMOD AND PDT: REPORT OF TWO CASES

Extramammary Paget disease is a rare intraepithelial adenocarcinoma, which can be associated with underlying adjacent or remote malignancies. Standard of care is currently surgical excision with wide margins. Despite wide local excision, recurrence is common. Furthermore, wide local excision can result in permanent dysfunction and discomfort. In previous studies, nonsurgical treatments with either photodynamic therapy (PDT) or topical imiquimod were reported. Another study demonstrated successful treatment with these 2 agents given in combination. The authors of this report offer a second published work on combination treatment with PDT and imiquimod in 2 patients. Complete remission was achieved in both, with multiple posttreatment biopsies. The authors speculate that there is a synergistic relationship between the 2 modalities, leading to the enhanced efficacy of the combination therapy. The authors suggest combined PDT-imiquimod therapy as a reasonable alternative to surgery in cases of extensive extramammary Paget disease in which the surgical procedure is not feasible or carries the risk for functional impairment.

Apalla Z, Lallas A, Tsorova A, et al. Complete response of extramammary Paget's disease with imiquimod and PDT: report of two cases. Photodermatol Photoimmunol Photomed. 2018;34:273-275.

HERPES SIMPLEX VIRUS SHEDDING RATE: SURROGATE OUTCOME FOR GENITAL HERPES RECURRENCE FREQUENCY AND LESION RATES, AND PHASE 2 CLINICAL TRIALS END POINT FOR EVALUATING EFFICACY OF ANTIVIRALS

The authors highlight the challenge of using the usual clinical endpoints, such as duration of recurrences or recurrence frequency, in the evaluation of efficacy of drugs used in the treatment of herpes simplex. Genital herpes lesions are highly variable in frequency and duration. Average frequency of recurrences is low, with most symptomatic patients having a median number of 4 recurrences/year. Defining lesion healing is an imprecise exercise. In this article, the authors evaluated the usefulness of the measurement of herpes simplex virus (HSV) shedding as a surrogate outcome for genital herpes recurrences. They examined the association of shedding with clinical outcomes, the consistency of HSV shedding, and whether shedding is in the causal pathway to lesions and recurrences. Among 674 participants, genital HSV shedding was detected on 17% of days, and genital lesions were reported on 10% of days. HSV shedding rates were strongly correlated with lesion rates. The association between medication and recurrence was reduced after adjusting for HSV shedding rates. When controlling for lesion shedding, much of the observed antiviral drug effect on

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Funding sources: None.
Conflicts of interest: None disclosed.
Accepted for publication September 26, 2018.

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Published online October 1, 2018.
J Am Acad Dermatol 2019;80:296-300.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.09.028

recurrences was explained by the extent of HSV shedding. In the case of the antiviral drug pritelivir, viral shedding accounted for 82% of the treatment effect, and obviated the statistical significance of the study. In the case of acyclovir/valacyclovir, viral shedding accounted for 41% of the treatment effect, and statistical significance, though attenuated, was maintained. The authors conclude that HSV shedding as measured by PCR is an appropriate surrogate outcome in assessing drug efficacy for treatment of herpes simplex. They also observed that shedding rates, which differ among individuals, appear to be consistent and persistent in individual patients, akin to what they compare to the set point of other chronic viral diseases, such as HIV and hepatitis B and C viruses.

Agyemang E, Magaret A, Selke S, Johnston C, Corey L, Wald A. Herpes simplex virus shedding rate: surrogate outcome for genital herpes recurrence frequency and lesion rates, and phase 2 clinical trials end point for evaluating efficacy of antivirals. J Infect Dis. 2018 Jul 17. https://doi.org/10.1093/infdis/jiy372.

THE INCIDENCE OF PEDIATRIC MALIGNANT SOFT TISSUE TUMORS OF THE SKIN AND SUBCUTANEOUS TISSUE

Using data from the 2000-2014 Surveillance, Epidemiology and End Results 18 database, the authors searched for cases of intermediate or malignant soft tissue tumors diagnosed in persons 0-19 years of age and identified 12 malignant soft tissue tumor types, which initially presented in the skin or subcutis of children in >50% of cases. The authors note that malignant soft tissue tumors disproportionately affect children; they comprise 7.4% of all pediatric cancers as opposed to 1.5% of adult cancers. The authors list commonly recognized malignant soft tissue tumors, such as dermatofibrosarcoma protuberans, Kaposi sarcoma, and leiomyosarcoma. They also discuss infantile fibrosarcoma and malignant rhabdoid tumor, which most frequently present in children <12 months, and identify a higher number than expected of alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma, and synovial sarcoma, which presented in the skin or subcutis. The authors stress that although malignant soft tissue tumors are rare in children, cutaneous or subcutaneous presentations are not. They stress the need for vigilance, citing the average time from presentation to diagnosis of pediatric dermatofibrosarcoma protuberans as 4 years and that, in 20 cases of pediatric leiomyosarcoma, a malignancy was only suspected in 2 cases before biopsy.

Liszewski W, Maguiness S, Greengard E, Boull C. The incidence of pediatric malignant soft tissue tumors of the skin and subcutaneous tissue. Pediatr Dermatol 2018 Sept 14. https://doi.org/10.1111pde.13669.

SURVIVAL OF CHILDREN AND YOUNG ADULTS WITH SKIN CANCER: ANALYSIS OF A POPULATION-BASED FLORIDA CANCER REGISTRY: 1981-2013

The authors cite several epidemiologic studies, including Surveillance, Epidemiology and End Results data from 2006-2009, reporting on an increase in rates of pediatric melanoma in the United States. Linking data from the Florida Cancer Data System and the 2000 US Census, the authors set out to determine skin cancer burden, distribution, and survival disparities in pediatric patients with melanoma. Of 1543 patients, there were 191 deaths from melanoma. Survival rates from time of diagnosis were 95.1% at 1 year, 87.2% at 3 years, and 81% at 5 years. Young adults (20-24 years) accounted for most of the cohort of 1543 skin cancers, accounting for 63.5% of the cases, followed by adolescents (10-19 years) at 31.8%, and children (0-9 years) at 4.7%. Within each subgroup, there was a trend for increasing incidence with increasing age. Among children, incidence of melanoma was higher in boys (52.1%), but among adolescents (55.5%) and young adults (61.1%), incidence was higher in female patients. Whites were at greater risk than people of color in all 3 age groups. The study data showed that 1-year survival was 77.9% for blacks and 91.5% for whites. Average 3–5-year survival in the 2 groups was comparable. The authors stress the need for identification of at-risk pediatric and young adult populations in designing targeted skin cancer recognition and prevention programs.

Dunn E, Moore K, Miao F, Kirsner R, Koru-Sengal T. Survival of children and young adults with skin cancer: analysis of a population-based Florida cancer registry: 1981-2013. Pediatr Dermatol 2018;35(5):597-601. https://doi.org/10.1111/pde.13588.

FIRST-IN-HUMAN TOPICAL MICROBIOME TRANSPLANTATION WITH *ROSEOMONAS MUCOSA* FOR ATOPIC DERMATITIS

In a previous study, the authors collected isolates of the human cutaneous commensal bacteria *Roseomonas mucosa* from healthy volunteers and

from volunteers with atopic dermatitis (AD). In that study, they found that in mouse models, the application of *R. mucosa* from healthy volunteers improved AD, and the application of *R. mucosa* from patients with AD exacerbated AD. In the present study, the authors tested this hypothesis with humans. In an open-label phase 1/2 study of 10 adults and 5 children with AD, topical application of *R. mucosa* strains from healthy volunteers decreased AD symptoms, lowered *Staphylococcus aureus* carriage, and improved quality of life. There were no adverse effects. The authors speculate that strain-level differences in *R. mucosa* in the 2 populations might account for the differing outcomes. In an ongoing trial of topical *R. mucosa* therapy in a cohort of pediatric patients, the authors are presently assessing changes in host serum markers, skin metabolomics, and skin microbiota by culture and genomic methods. They hope to establish a causal and mechanistic basis for the preliminary benefit seen with topical microbiome transplantation, which will lay the groundwork for larger, placebo-controlled trials.

Myles I, Earland N, Anderson E, et al. First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. JCI Insight. 2018;3(9). pii:120608.

THE ANTI-INFLAMMATORY ACTIVITIES OF *PROPIONIBACTERIUM ACNES* CAMP FACTOR-TARGETED ACNE VACCINES

CAMP (Christie-Atkins-Munch-Petersen) factor is a pro-inflammatory virulence factor secreted by *Propionibacterium acnes* (now called *Cutibacterium acnes*). These authors use an ex vivo acne model to demonstrate the importance of CAMP factor in acne pathology and highlight a potential therapeutic target. Injection of wild-type *P. acnes* into mouse ears induced significantly more redness, swelling, and cytokine production than knockout CAMP *P. acnes*, supporting the role of CAMP in acne inflammation. A monoclonal antibody to CAMP factor significantly reduced the production of inflammatory cytokines, including interleukin 6, in human acne ex vivo explants. They suggest that the principles underpinning this work point toward the possibility of acne immunotherapy.

Wang Y, Hata T, Tong Y, et al. The anti-inflammatory activities of *Propionibacterium acnes* CAMP factor-targeted acne vaccines. J Invest Dermatol 2018 Jun 30. https://doi.org/10.1016/j.jid.2018.05.032.

FREQUENT BASAL CELL CANCER DEVELOPMENT IS A CLINICAL MARKER FOR INHERITED CANCER SUSCEPTIBILITY

The authors hypothesized that patients experiencing multiple basal cell carcinomas (BCCs) as a result of ultraviolet light–induced mutagenesis in the skin might, on analysis, show early deficiencies in DNA repair, which in turn might reflect increased risk not just for BCCs but also for other cancers. The appearance of frequent BCCs could then, by being a clinical marker of underlying defects in DNA repair, help identify patients with an increased risk for other cancers. To investigate this hypothesis, the authors assessed the prevalence of germline mutations in 29 cancer susceptibility genes among patients who developed unusually frequent BCCs, in a cohort constituting the top 5% of individuals with BCC seen at the Stanford Hospital and Clinics. The authors found in these patients a statistically significant increase of inherited mutations in DNA repair genes. These same patients were found to be at increased risk of developing other malignancies; 34.4% of the frequent BCC cohort had a personal history of additional cancers, including 5 invasive melanomas and 5 hematologic, 2 breast, 2 colon, and 5 prostate cancers. Compared with the Surveillance, Epidemiology and End Results–estimated prevalence of any cancer in a comparable ethnic and age cohort, the frequent BCC cohort had a relative risk of 3.5 (95% CI 2.5-4.9) for any cancer. The authors suggest frequent BCC development as a clinical sign of inherited cancer risk, reflecting the higher prevalence of inherited mutations in DNA repair genes in such patients, which in turn predisposes these same patients to a higher risk of developing other malignancies, both cutaneous and internal.

Cho H, Kuo K, Li S, et al. Frequent basal cell cancer development is a clinical marker for inherited cancer susceptibility. JCI Insight. 2018;3(15):e122744. https://doi.org/10.1172/jci.insight.122744.

AN INTERNATIONAL COMPARISON OF GOOGLE SEARCHES FOR SUNSCREEN, SUNBURN, SKIN CANCER, AND MELANOMA: CURRENT TRENDS AND PUBLIC HEALTH IMPLICATIONS

Google Trends is a Google website that analyzes the popularity of top Google search

queries across various regions and languages. The authors analyze Google Trend data to help gauge public interest in skin cancer and skin cancer prevention and to identify propitious times to engage in public awareness campaigns. They note that Google Trend can reveal the effectiveness of public awareness campaigns, using as an example a measured significant spike in searches for the term "breast cancer" during the Pink October breast cancer awareness campaign in Great Britain. Their findings in this study are varied, and findings in the 5 countries studied—the United States, the United Kingdom, Canada, Australia, and New Zealand—are not necessarily congruent. For all 5 countries, the popularity of "sunscreen" and "sunburn" searches has increased, whereas "skin cancer" and "melanoma" searches have decreased in all countries except the United Kingdom. The authors note that "skin cancer" and "melanoma" searches peak during winter months, and "sunscreen" and "sunburn" searches peak during summer months. "Sunburn" was the most popular search term overall. For all countries studied, the search terms "sunscreen" and "sunburn" were highly correlated and increasing in popularity. Search volumes for these 2 terms were higher than search volumes for "skin cancer" or "melanoma." For most countries, with the exception of New Zealand, there was a positive correlation between the terms "sunscreen" or "sunburn" and melanoma incidence.

Using these data, the authors suggest that public education campaigns should target skin cancer/melanoma in the winter, when searches for these terms—and by proxy, public interest—is higher. They also suggest that the words sunscreen and sunburn should be targeted as key words for skin cancer prevention campaigns.

Hopkins Z, Secrest A. An international comparison of Google searches for sunscreen, sunburn, skin cancer, and melanoma: current trends and public health implications. Photodermatol Photoimmunol Photomed. 2018 Sep 10. https://doi.org/10.1111/phpp.12425.

MELANOMA UNDERREPORTING AMONG US DERMATOPATHOLOGISTS: A PILOT STUDY

The author addresses the problem of melanoma underreporting in the United States. In response to an anonymous online survey of dermatopathologists, 34% of dermatopathologists responded no to the question "Do you believe that you are obligated to report new diagnoses of melanoma to your state cancer registry?" Also, 35% of dermatopathologists responded no or I don't know to the question "Do you or does anyone in your practice report melanoma diagnoses (new or established) to a cancer registry?" Interestingly, the author notes that although the 2 responses were highly correlated, they were not mutually exclusive. Two nonbelievers were reporters, and 3 nonreporters were believers.

The author lays out some of the challenges to securing valid data on the number of melanoma cases in the United States. Many melanomas are diagnosed in an office, not a hospital-based setting. In a 2011 survey, half of practicing dermatologists were unaware of the requirement to report melanomas, and 56% did not actively report their diagnoses. Up to one third of dermatologists interpret their own biopsy specimens. The author concludes that there is a lack of consensus on who is responsible for reporting melanomas, and the absence of adequate incentive for either dermatologists or dermatopathologists to do so.

Heuring E. Melanoma underreporting among US dermatopathologists: a pilot study. J Cutan Pathol. 2018;45:550-555.

OVERALL SURVIVAL IN PATIENTS WITH *BRAF*-MUTANT MELANOMA RECEIVING ENCORAFENIB PLUS BINIMETINIB VERSUS VEMURAFENIB OR ENCORAFENIB (COLUMBUS): A MULTICENTRE, OPEN-LABEL, RANDOMISED, PHASE 3 TRIAL

During December 30, 2013-April 10, 2015, a total of 577 patients with *BRAF*-mutant cutaneous melanoma that was histologically confirmed, locally advanced, and unresectable or metastatic were randomly assigned to 1 of 3 treatment arms: encorafenib (BRAF inhibitor) and binimetinib (MEK inhibitor) combined, vemurafenib (a BRAF inhibitor) alone, or encorafenib alone. The patients had to be ≥18 years of age and could be either treatment naïve or having progressed on or after first-line immunotherapy. Median follow-up for overall survival was 36.8 months. Median overall survival was 33.6 months in the combination encorafenib and binimetinib group, 23.5 months in the encorafenib group, and 16.9 months in the vemurafenib group. Progression-free survival was 14.9%, 9.6%, and 7.3% for the combination group, encorafenib group, and vemurafenib group, respectively. The authors propose combination therapy as a new benchmark against which BRAF-MEK inhibitor therapies for *BRAF*-mutant melanoma can be measured.

Dummer R, Ascierto P, Gogas H, et al. Overall survival in patients with *BRAF*-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19(10):1315-1327. https://doi.org/10.1016/S1470-2045(18)30497-2.