Controversies Surrounding Pigmented Lesion Biopsies

Dirk M. Elston, MD

Introduction. "There are situations in which how we biopsy makes a difference that can profoundly affect the interpretation of the specimen," Dr. Elston stated, speaking from his 30 years of practice as both clinician and dermatopathologist. Most often, an inadequate biopsy specimen delays diagnosis. Less frequently, but of far greater importance, is a mistaken diagnosis. Elston focused on four pigmented lesions—acral nevus, Spitz nevus, lentigo maligna, and dysplastic nevus—that are particularly vulnerable to inadequate biopsy and for which an incorrect diagnosis carries serious consequences.

Acral Nevus. In an acral nevus, linear nests follow the dermatoglyphs and the lesion must be bisected across them. When bisection is parallel to the dermatoglyphs, the histologic appearance becomes one of confluence with long, irregular nests and an inaccurate rete ridge pattern, simulating melanoma. Illustrating how critical this is, Elston described a study in which a bisected acral nevus was shown to 10 excellent university-based surgical pathologists. Half of the lesion was bisected correctly, and a separate slide was made with the other half bisected incorrectly (parallel to the dermatoglyphs). The half that was correctly bisected was unanimously called benign, while the half that was bisected parallel to the dermatoglyphs—the same lesion—was unanimously diagnosed as melanoma, misdiagnosed based purely on the plane of section.

An acral melanocytic lesion should be completely excised with a narrow margin, using saucerization or scooping it out to reduce morbidity on an acral site. Do the bisection yourself if necessary to ensure that it is bisected across the dermatoglyphs, and write on the bottle that it has already been bisected.

Spitz Nevus. The majority of Spitz nevi can be diagnosed in H&E sections, but the three most predictive features are at the lesion’s sides and base—areas often not included in the biopsy specimen. At the base, a Spitz nevus disperses into single file while spitzoid melanomas remain as a large aggregate. A Spitz nevus rarely contains deep mitoses, while spitzoid melanomas may have mitoses or atypical mitotic figures. And a Spitz nevus shows sharp lateral circumscription, ending in a nest, while malignant lesions trickle off with individual cells. Because this lesion’s sides and base are often omitted, immunostains and genome analysis may be needed.

Also In This Issue

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Michael D. Tharp, MD,
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Biopsy Technique Errors Leading to Misdiagnosis

Left: If this benign acral nevus is bisected parallel to the dermatoglyphs instead of across them, it could be misdiagnosed as melanoma. Right: Because each color in this mottled lesion of lentigo maligna may reflect a different pathology, sample each color to avoid sampling error and misdiagnosis.

(Continued on page 3)
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Dr. Elston illustrated this with a highly pleomorphic, purely epithelioid lesion from an 11-year-old girl that lacked both the spindle cells typical of a Spitz nevus and the junctional component typical of a primary melanoma. A lesion removed 3 years earlier was highly atypical and since then, atypical serial lesions in the regional drainage basin had appeared. Because of the transected base immunostaining proved to be helpful, confirming a high proliferative fraction and poor staining with S100A6.

**Lentigo Maligna (LM).** Almost half of all cases of lentigo maligna occur in collision with a pigmented actinic keratosis or benign lentigo, and each color in a mottled lesion may actually represent a different pathology. Unless the biopsy method demonstrates each morphology within the lesion, the risk of sampling error is extremely high. Elston documented this in two studies. One study inspected 96 Mohs debulking specimens and 51 broad shave biopsies of LM that contained only the clinical lesion, with no adjacent sun-damaged skin. Almost 50% were in collision with a second pigmented lesion—mostly a benign solar lentigo or pigmented AK—in at least one-fifth of the lesion. The darkest area merely represented the greatest pigment incontinence, not the greatest likelihood of demonstrating the melanoma. The second study demonstrated that lichenoid regression within lentigo maligna can easily be interpreted as benign lichenoid keratosis.

Use of a 4-mm punch biopsy in the setting of LM is associated with up to an 80% risk of a false negative biopsy result. In a biopsy for LM, “one needs a significant area of the dermoeidermal junction.” Elston recommends either a very broad, paper-thin shave biopsy or his personal preference—a small shave of every color in the lesion. All pieces go in the same bottle and are processed as a single specimen.

**Dysplastic Nevus.** Beginning a shave biopsy at the edge of the visible brown border actually truncates the lesion, and as most of the atypia and confluence are at the outer edge, pathologists may “upgrade” the lesion when it extends broadly to a margin. For the best assessment of margins and eliminating diagnostic problems, a saucerized biopsy technique can be used to remove the lesion plus a border of 0.5–2 mm of normal-appearing skin. This does little to affect the final appearance of the wound, but can have a profound effect on the pathology report.

**Food for Thought**

Until molecular techniques replace H&E—how best to help your pathologist help you and your patient....

- Acral nevus
  - Bisect across dermatoglyphs
- Spitz nevus
  - Complete excisional biopsy
- Lentigo maligna
  - Broad shave, multiple biopsies
- Dysplastic nevus
  - Saucerization biopsy with 0.5–2 mm margin

**MINI-SYMPOSIUM: REVISITING OLD THERAPIES**

**Clam(p)s and (Surgical) Pearls**

**Christopher J. Arpey, MD**

**Introduction.** Dr. Arpey reviewed four “simple, practical approaches to common surgical scenarios” that benefit both dermatologist and patient, are negligible in cost, and often improve time efficiency.

-The Delayed Tie. Arpey described wounds requiring buried absorbable sutures but with inadequate space for inserting the needle for the last suture. This occurs with concave areas (e.g., the melolabial fold and postauricular sulcus), areas under excess tension and reduced mobility (e.g., scalp, upper back), and tight quarters (e.g., interdigital spaces). Place and tie all but the final two buried sutures. On the next-to-last suture, exit the dermis but do not yet tie the knot. Clamp the untied ends so they are easily identifiable (especially if delay-tying more than one suture). Place the final suture, tie that knot, then release the clamp and tie that next-to-last suture.

-Braided Coated Polyester Suture. Use this instead of polypropylene or nylon sutures for friction-prone areas (body folds, lips, inguinal and axillary creases, the genital region, flexural areas, web spaces, and palms and soles) and atrophic fragile skin (the dorsal hand, in the elderly, in steroid-induced atrophy, or post-trauma). This superficial nonabsorbable suture is much softer for the patient, handles like silk (but is not a foreign protein and thus less likely to cause inflammation), and less likely to tear skin.

**Thin, Sensitive, Frictional: Lips**

**Which suture would you rather lick and speak over for a week?**

- Braided Polyester
- Nylon
**Pigskin Xenografts.** These sterilized biological dressings—basically, split-thickness skin grafts—derived from pigs, frozen or vacuum-packed, are inexpensive, easy to care for, and especially useful for elderly, debilitated, or squeamish patients. Shelf life is 18 months. Although these grafts do take extra time to suture, may become malodorous, and may require replacement at follow-up, their benefits are predominant. They require no wound care, allow granulation underneath, can last 7–10 days (sometimes longer), can be replaced without limit, and may predict autologous graft survival. Arpey discussed his technique and preferred product.

**Gentian Violet.** This inexpensive FDA-approved OTC vital dye is seeing new advocacy for its antiangiogenic, desiccant, and antimicrobial properties. Arpey uses it most frequently to halt exuberant granulation tissue during wound healing, after eschar removal if the patient is not cleaning the wound well, and as an adjunct for treating some pyogenic open wounds.

### Choosing Topical Retinoids for Aging Skin

*Dana L. Sachs, MD*

**Introduction.** Retinoic acid (RA) binds to and activates retinoic acid receptors (RARs), inducing transcriptional activation of RA-responsive genes to produce tissue-specific biologic responses. In the skin this involves procollagen synthesis. Dr. Sachs discussed natural retinoids, their metabolism, the known and suspected antiaging effects of their topical therapeutic use, and what to recommend to patients until we know more.

**Aging Skin.** Both UV light and intrinsic aging increase reactive oxygen species (ROS) in skin, which generate self-perpetuating cycles of collagen degradation. ROS increase the critical collagen-degrading enzyme collagenase (ie, matrix metalloproteinase 1), thus increasing collagen fragmentation and loss of the mechanical tension on fibroblasts that stimulates them to express procollagen. Altered signaling from collapsed shrunken fibroblasts further increases ROS production and also blocks the TGF-β pathway, further increasing collagenase synthesis. Intervening to improve skin appearance involves restoring mechanical tension on fibroblasts directly, or by stimulating the TGF-β pathway to block collagenase and increase procollagen synthesis. Interestingly, retinoids stimulate this pathway.

**Retinoids.** This group of agents includes RA (*aka* tretinoin) plus retinol (ROL, ie, vitamin A), retinaldehyde (RAL), and retinyl esters (RE, the major storage form of retinol in the epidermis). ROL converts to RAL, then to RA (which binds with the RARs). RAL also converts to RE. ROL and RE constitute 99% of the skin’s retinoid content; RA and RAL represent <1% each. In the first several weeks of topical RA or ROL therapy, glycosaminoglycans are observed in the epidermis to soften and smooth the skin. Within the first week of therapy, the stratum corneum’s basket-weave configuration disappears as it compacts, and the epidermis becomes hyperplastic and slightly spongiotic. After 4 months, improved collagen production begins to diminish wrinkles (collagen’s 15-year half-life creates long-standing improvement). Discoloration—dyspigmentation, hyperpigmentation, lentigines—diminishes substantially over 10 months of treatment. The typical rapid appearance of retinoid dermatitis—which Sachs prefers to call *retinoic acid dermatitis*, as retinol does not cause this—is “the major barrier to patient compliance.”

### Retinoid Metabolism

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### ROL 0.4% Improves Skin–Age 90

*Baseline*  

*Month 6*  

*Procollagen*

**Conclusion.** The retinoids are photolabile but *not* phototoxic. Retinoic acid and the less-irritating retinol have the most data supporting their use at this point, although dosing and optimization regimens are still “a big mystery.” Studies to clarify these considerations are underway. For now, helping patients titrate these agents is the best way to avoid dermatitis and continue treatment.

**Isotretinoin: Facts & Fallacies**

*Seth J. Orlow, MD, PhD*

**Introduction.** Although isotretinoin—approved for use in patients with treatment-resistant nodulocystic acne in 1982—remains the most effective therapy and the only one proven to cause prolonged or permanent remissions, its risk-benefit profile reserves it for the more severe end of the acne spectrum, ie, patients who have failed to respond to topical and accepted oral therapy. Teratogenicity is a particularly well-known and documented risk, although the window of its activity during human pregnancy has not been clearly defined. Dr. Orlow also discussed laboratory abnormalities, mucocutaneous changes, ocular changes, GI changes, musculoskeletal changes, and neuropsychiatric changes, focusing primarily on areas with conflicting evidence and the questions thus raised.

(Continued on page 7)
The Dermatology Foundation will be celebrating its 50th anniversary next year—how has it helped the specialty become what it is today?

“The DF is an incredibly important foundation. For nearly 50 years, it has helped forge the science of our specialty through the development of new dermatologists and investigators dedicated to teaching and research. During this time, the Foundation has allocated nearly $70 million to dermatologic research, awarding over 1,800 grants, fellowships, and career development awards. Outside of the NIH, the DF is the country’s largest supporter of dermatologic research.

“In a recent survey of 181 of our career development award recipients, we determined that an incredible 80% currently hold full or part-time academic appointments. Equally impressive is the fact that 84% of them went on to receive independent research dollars, with 86% from highly competitive federal grants. These individuals received NIH support totaling at least $318 million, which translates to a minimum of $10 of federal research funds realized for every $1 of DF support. This is quite an exceptional return on investment.”*

What are your thoughts on the more immediate challenges ahead for the specialty’s development (eg, the economy, federal funding, and Obamacare) and how they will affect the role of the DF?

“It is clear the future holds significant challenges for every physician in the field. For new investigators, money is and will remain tight. Federal research grants have been significantly reduced and will undoubtedly continue to decline; the actual amount of available dollars and their allocation also remains uncertain. That is why the DF’s mission to identify and support young basic and clinical scientists has become even more important to our specialty. Given this pessimistic outlook for federal funding, the Foundation will require much greater support from the dermatologic community to meet the specialty’s funding needs.”

What are your goals for the DF?

“Several years ago, while he was president of the DF, Dr. Bruce Wintroub expressed a strong desire to double the research award dollars given by the DF each year. It is a very challenging goal, and I embrace it and think it is within our reach. The DF awarded $3.2 million in research funds last year. Imagine the power of having over $6 million to support dermatologic research each year. If every dermatologist became a DF member, this goal could easily become a reality. And just imagine how many more people and important projects could be supported by these dollars.”

Why is it important to be a member of the DF?

“Every dermatologist should be a member of the Foundation. The DF offers a wonderful opportunity to contribute to the specialty that has given, and will continue to give, each of us so much. Becoming a member of the Foundation empowers dermatologists to help shape the future of this great specialty for many years to come. For myself, I can’t think of a better way to spend my money—and my time.”

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Laboratory Abnormalities. Guided by the package insert, many physicians routinely test patients, looking for hepatotoxicity, lipid elevations, leukopenia, and thrombocytopenia. These assertions are based on old clinical trials, however, and their magnitude is not supported by more recent retrospective studies. In essence, elevated triglycerides are the most common laboratory abnormality noted in patients on isotretinoin; levels typically return to normal after treatment.

Ocular Changes. Orlow noted significant flaws in studies describing the prevalence of isotretinoin-associated ocular adverse effects, but that, despite this, there is consensus that “some of these effects do seem to be associated with the medication.” Because persistent decreased dark adaptation has been recently documented in retrospective testing, Orlow asked hypothetically if isotretinoin use should rule out a career in flying, and if electro-physiologic screening should be done in professions for which night vision is critical.

Inflammatory Bowel Disease. Conflicting evidence has existed concerning a link between isotretinoin use and IBD and, among positive studies, the types of IBD involved. A substantial study just published by Etminam and colleagues, however, does not suggest any increased risk for IBD of any type in this context. Recently, adjusting for prior tetracycline use and comparing isotretinoin to other acne treatments and no treatment suggest that acne itself may be the risk factor rather than isotretinoin, and that prior antibiotic use may play some role.

Isotretinoin and IBD: Population-based Study Suggests Association With Acne?

- Retrospective population-based cohort study of all residents of British Columbia 12–29 yrs over 12 yrs
- 46,922 treated with isotretinoin, 184,824 treated with topical acne medication and 1,526,496 untreated
- No significant association between IBD and isotretinoin use when adjusted for prior tetracycline use
  - Compared to untreated, rate ratio (95% CI) for isotretinoin 1.14 (0.92–1.41), for topical acne therapy 1.11 (0.99–1.24). “Weak but significant association” in 12–19: RR 1.39 (1.03–1.87)
- Topical therapy use associated with higher risk of UC:
  - RR1.19 (1.00–1.42), suggesting acne is the risk factor
- “Risk of IBD with isotretinoin similar to that with topical acne medications”

For Isotretinoin and IBD—Questions Include....

- What is the contribution of antibiotic use?
- What is the contribution of acne itself?

Musculoskeletal Changes. Although muscle-related complaints and high CPK levels have been reported in 15–50% of acne patients treated with isotretinoin, most cases have been associated with vigorous physical activity in adolescents. An increased incidence of osteophytes and bony bridge formation, especially in the spine, is clearly associated with isotretinoin use, and the development of hyperostosis (aka DISH)—seen primarily with extended high-dose treatment for patients with disorders of cornification—is dose- and time-dependent.

KEYNOTE ADDRESS

The Emerging Periodic Table of Melanocytic Neoplasia

Boris C. Bastian, MD

Introduction. Dr. Bastian presented a proposal for classification of melanocytic neoplasms that integrates the rapidly emerging molecular landscape with the multifaceted clinical and histopathological aspects. It is intended to provide a framework to guide clinical management and research studies. The current WHO classification system has had limited impact on the way melanoma is treated. Bastian discussed the existence of some of the biologically distinct classes in his classification schema, which put to rest the long-standing debate over the pathogenetic role of UV radiation. Recent genetic studies reveal UV radiation as the dominant pathogenetic factor that shapes the genomes of certain classes of melanocytic neoplasms, while other, yet-to-be-discovered, factors are involved in others.

The Basic Patterns. Several independent studies have shown that tumors arising on body sites that received large cumulative doses of UV radiation differ from those on less-exposed sites. The degree of solar elastosis in the adjacent skin has emerged as the single most powerful criterion to distinguish between these two main categories.

Genotype–Phenotype Correlations in Primary Melanomas

Melanomas on skin without marked solar elastosis (nonchronic sun-damaged skin or non-CSD melanomas) arise on intermittently sun exposed skin in significantly younger patients who tend to have many melanocytic nevi. Roughly 70% of both the nevi and the melanomas in this category harbor BRAF V600E mutations. The occurrence of multiple neoplasms with these mutations in a given individual indicates that a specific sensitivity put melanocytes at risk to acquire these mutations during a limited time period early in life. Compared to chronically sun exposed tumors, the melanocytes in these tumors are more pigmented, larger, and round rather than spindled. They have more upward scatter and tend to form nests, are more circumscribed at the edges rather than spreading laterally and diffusely, and the epidermis is thickened rather than atrophic.

Dysplastic Nevi. On an individual with many acquired nevi, the nevi tend to be very similar, including in size. Nevus size is also much more concordant between monozygotic than dizygotic twins. This reflects the existence of heritable variations in a menu of factors that restrain the expansion of melanocytes with acquired mutations in oncogenes (such as BRAF). The inherited genotype determines which barriers are intact, or partially or not intact, and this combination determines nevus size and multiplicity. Individuals with a complete series of barriers experience no proliferation, and no nevi. With various combinations (see illustration above), the result could be many small nevi, or a few large (ie, dysplastic) nevi, or many large nevi. Once cells within such a nevus have bypassed the final barrier, melanoma ensues. Thus “this phenotype of clinically dysplastic nevi is fully sufficient to establish a patient’s increased risk for melanoma, as the increased nevus size reflects that all the patient’s melanocytes have inherited a partial barrier defect. There is nothing that histopathological assessment can add to this conclusion. Thus there is no need to biopsy a nevus to determine whether it is dysplastic—and thus indicative of an increased melanoma risk. We only need to biopsy lesions that have become suspicious for melanoma.”

Biopsy:
- The phenotype of clinically dysplastic (enlarged) nevi is sufficient to establish that a patient has an increased melanoma risk. NO BIOPSY IS NEEDED to support this conclusion.
- BIOPSY IS NEEDED only for lesions that are clinically suspicious for melanoma.

What’s Causing This Leg Ulcer?
Mark D.P. Davis, MD

Introduction. Although wound care is important for the care of leg ulcerations (ulcer), that alone is generally insufficient for the ulcer to heal. The underlying cause must be addressed. Thus an ulcer ‘should be regarded as a physical sign, not a final diagnosis, and one needs to ask: what is the diagnosis, what is the reason for this ulcer?” Why? Because the diagnosis guides appropriate treatment of the ulcer’s cause, and that is fundamental to successful wound healing.

Germline Mutations of BAP1 May Predispose to Uveal and Cutaneous Melanoma

The genetically and clinically distinct presentation of CSD melanomas arises in older patients. In the comparatively fewer BRAF mutations, V600K predominates over V600E, and another ~10–15% of cases harbor activating KIT or NRAS mutations. This type of sun-related melanoma needs a very high cumulative dose of UV to manifest itself, which takes time to accumulate. This explains why these patients are older, and why these melanomas occur primarily in anatomic sites with the greatest sun exposure.

Acral melanomas arise on non-hair-bearing skin and the nail apparatus. They also have less frequent BRAF mutations, and instead harbor mutations and/or amplifications of KIT and amplifications of cyclin D1 mutations. Mucosal melanomas share the high frequency of amplifications with acral melanoma, but with other genomic regions primarily affected. As opposed to most other cancers, these gene amplifications occur very early during cancer progression. The cause of the unusually high degree of genomic instability in both acral and mucosal melanoma remains to be discovered.

Using fluorescence in situ hybridization in biopsy tissue provided a stunning discovery that Bastian illustrated with two patients. In one patient, stretches of clinically and microscopically normal skin adjacent to acral melanomas harboring gene amplification showed single basal melanocytes that shared similar amplifications, although at a lower copy number. These “field cells” likely represent a subtle extension of melanoma in situ that cannot be recognized by conventional methods. The second patient had two clinically and microscopically distinct melanomas on the palm, one invasive and one in situ. Fluorescence in situ hybridization revealed that both lesions arose within a larger area in which melanocytes had amplification of cyclin D1, and thus were actually part of the same lesion. “This was actually a single melanoma, like a submerged iceberg with two tips that had broken through the clinical detection horizon.” The subtle extension of the melanoma characterized by the presence of field cells likely would have taken years to decades to develop into overt melanoma in situ.
Although ulcerations of the skin are most commonly vascular (predominantly venous) or neuropathic, dermatologists can help to recognize the more unusual causes. The etiologies of leg ulcers can be classified into broad categories: vascular, neuropathic, due to trauma, infection, inflammatory conditions (such as connective tissue diseases), neoplasm, drugs/medications, and some unusual causes such as pyoderma gangrenosum. “Remember that leg ulcerations are often multifactorial.” A “diabetic” foot ulcer, for example, a term used for an ulceration occurring in the setting of diabetes mellitus, typically involves a varying combination of arterial insufficiency, diabetic neuropathy, and local trauma. Dr. Davis shared case examples from a number of categories.

**Keys to Management—Common Ulcers.** For a classic **venous ulcer**, the key for management is leg compression to eliminate edema. Use compression wraps, eg, ACE wraps, until swelling resolves, then measure for sufficiently snug support stockings. For an **arterial ulcer**, the key to management is revascularization. For a **neuropathic ulcer**, the key to resolution is off-loading the wound.

**Causes of Ulcers**

- Vascular  
  - Venous  
  - Arterial  
  - Small vessel  
  - Vasculitis  
  - Occlusion  
- Neuropathic  
- Trauma  
- Infection  
- Malignancy  
- Inflammation  
- Connective tissue Dx  
- Drug-induced  
- Pyoderma gangrenosum

(As of August 22, 2013)

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**OHIo**

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**FROM THE PUBLIC**

| Richard J. Havens |
Antimicrobial treatments for fungal infections, such as blastomycosis, may require prolonged and treative antimicrobial therapy. Ulcerations due to trauma, such as habitual scratching—which typically produces linear ulcerations—stopping the scratching is key. For medication-caused ulcerations, stopping the medication is key. A classic example is hydroxyurea-induced ulcers, generally agonizing medication-caused ulcerations. For ulcerations caused by trauma (a habit), consider the use of oral immunosuppressants, such as systemic corticosteroids, although a wide variety of therapeutic approaches have been described.

Summary. Diagnosis and appropriate management of the underlying cause of a given leg ulceration is key to successful healing.

Life-Threatening Dermatoses

Dirk M. Elston, MD

Introduction. “These are scenarios in which what we do or fail to do makes a vast difference for the patient.” Dr. Elston discussed five illustrative patients.

Patient 1. This middle-aged woman had a seizure disorder and rash, “two terms with real potential for harm when they occur together.” The patient’s skin was sloughing off in sheets, with characteristic histology for toxic epidermal necrolysis. With a history of dilantin hypersensitivity, she had recently begun carbamazepine. A cross-reacting drug had unwittingly been prescribed. In a patient with a history of anticonvulsant hypersensitivity, it is critical not to use another aromatic, tricyclic, or gabapentin. Elston described the elements that improve the odds: excellent care in a burn center and GCSF to raise white blood cell count. IVIG data are mixed, but cyclosporine appears promising in small studies.

Patient 2. An 18-year-old with seizure disorder had a very different rash, with a sandpapery surface. This was part of a drug hypersensitivity syndrome, or DRESS (drug reaction with eosinophilia and systemic symptoms). The specific manifestations of DRESS vary by drug, and it is important to know the different profiles, which, Elston described.

Patient 3. A 53-year-old ice-cream vendor in his truck, hit by a drunk driver, suffered severe head trauma. He was on anticonvulsants for seizures and massive corticosteroid doses for cerebral edema, and had suddenly developed a fungal lesion within 4 hours. The rapid growth in a patient with steroid-induced hyperglycemia suggested a zygomycete, a sugar-devouring fungus that grows rapidly. Multiple debridement episodes guided by a tissue Gram stain plus systemic antifungal therapy with posaconazole can save a life.

Patient 4. A 22-week gestation infant developed depressed, scalloped, leathery eschars typical for fungal sepsis, and biopsy revealed black mold. Despite high-dose itraconazole and debridement—the one chance for survival—the infant died. Autopsy revealed fungal sepsis in all organs.

Patient 5. This comatose, febrile patient, after a recent cardiac catheterization, had developed a new murmur and skin lesions. The echocardiogram and repeated blood cultures were negative for endocarditis, but skin exam revealed a Janeway lesion resulting from a septic embolus from staphylococcal endocarditis. This was ultimately confirmed by a repeat transesophageal echocardiogram.

Controversies in Oral Contraceptive Use in Acne

Bethanee J. Schlosser, MD, PhD

Introduction. Adult acne affects 45–51% of women 20–30 years old, and ~12% of women 40–49 years old. Dr. Schlosser explained the influence of androgens and noted that anti-androgens—especially the combination (an estrogen with a synthetic progestin) oral contraceptive pills (OCP)—are an alternative acne treatment for women with moderate to severe acne.
**Giving Back—Profile of a DF Volunteer**

**“The DF Volunteers Inspire Me”**

It wasn’t until Mohs surgeon Dr. Kishwer Nehal attended her first Leader Society orientation that she “truly began to understand the DF’s strength,” she recalls. “The entire organization is based on dermatologists volunteering their time to support the specialty. I was struck by the commitment, dedication, and energy of our fellow dermatologists. They never lose their enthusiasm, and they’re truly inspirational.” This is the driving force behind the Foundation’s ability to provide early career research support each year.

Dr. Nehal heads the Mohs surgery program that she established at Memorial Sloan-Kettering Cancer Center in 1996, after completing her residency and then a Mohs fellowship at New York University. She joined the Dermatology Foundation in 2002 when a senior colleague invited her to become a Leaders Society member. “He clearly saw this as an organization that was important to the specialty and worth supporting, and I valued his view.” Five years later, she joined the New York State Leadership Society campaign, which she now leads. Since then she has also steadily increased her participation in the Foundation by joining the Annenberg Circle, and this year becoming an AC Sustaining member with a 10-year pledge.

When Dr. Nehal talks to colleagues about joining the Leaders Society, she points to the Foundation’s substantial role in helping young investigators become highly competitive for increasingly scarce federal research funds. “This is an era of shrinking health care dollars and grant money. If we don’t help our specialty move forward by supporting young dermatologists with great research ideas and skills—who will?” She also explains that she is quite impressed with the research award review and deliberation process. “Each award application is very critically reviewed—in a process similar to the one used for federal research funding.” Dr. Nehal loves to emphasize that DF award categories represent the full scope of modern dermatology, including “grants dedicated to surgery, outcomes research, human appearance, women’s health, and health care policy.”

Dr. Nehal, who was recently invited to join the Leaders Society National Campaign Committee, deeply values her work with the Foundation and her involvement with her fellow volunteers. “There is so much enthusiasm, commitment, and hard work. It’s very rewarding both professionally and personally.”

The DF is exceptionally grateful to its many volunteers who work hard and give generously of their time to keep dermatology at the forefront of medicine.

**Appropriate Patients.** Although the FDA specifies hormonal contraception for women who have failed topical anti-acne treatment and simultaneously desire contraception, “we consider a much wider group.” Clinical considerations include signs of hyperandrogenemia; late onset or persistent acne; prominence on the lower face, jaw, and neck; perimenstrual flare of acne; resistance to more conventional treatments; use in lieu of repeat isotretinoin.

**The Pill.** The estrogen component—ethinylestradiol typically 10–30 mcg per pill—reduces androgen synthesis. There are 10 synthetic progestins covering 4 generations. Most are derived from 19-nortestosterone. Drospirenone, a 4th-generation progestin and the newest in OCPs, derives from 17α-spiroloactone. OCPs currently FDA-approved for treating acne in women include Ortho Tri-Cyclen® (with 3rd generation norgestimate), YAZ® and Beyaz® (with 4th generation drospirenone), and Estrostep® (with 1st generation norethindrone acetate).

**Androgenic Index of Progestins**

<table>
<thead>
<tr>
<th>None</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drospirenone</td>
<td>Desogestrel (etonogestrel)</td>
<td>Norethindrone</td>
<td>Norgestrel</td>
</tr>
<tr>
<td>Norgestimate (norelgestromin)</td>
<td>Norethindrone acetate</td>
<td>Medroxyprogesterone acetate</td>
<td></td>
</tr>
<tr>
<td>Gestodene</td>
<td>Ethynodiol diacetate</td>
<td>Levonorgestrel</td>
<td></td>
</tr>
</tbody>
</table>
Effectiveness. Placebo-controlled studies of OCPs for moderate acne vulgaris show significant reduction in inflammatory, noninflammatory, and total lesion counts compared to placebo at 3 months, with still greater benefit seen at 6 months. In the updated Cochrane Review of randomized trials to date, combination OCPs uniformly outperformed placebo, with no significant differences noted between OCP formulations.

Important Questions. Does concurrent antibiotic use reduce OCP effectiveness? Data indicate that only antimicrobials stimulating CYP3A4 enzymes—ie, rifampin, rifabutin, and the antifungal griseofulvin—reduce serum estrogen levels and efficacy of OCPs. What is the risk for venous thromboembolic events (VTE)? Risk is higher in women >40 years old, at higher estrogen doses (50 mcg vs 30 mcg), and with tobacco use. Risk is highest in the first 6–12 months of OCP use and normalizes by 3 months after OCP discontinuation. The risk of VTE during pregnancy (8–12/10,000) and the first 3 months post-partum (≤30/10,000) far surpasses the risk of VTE with OCP use. The progestin factor has received recent focus for VTE risk stratification, but studies to date have significant limitations. A long-term cohort study currently in progress is expected to clarify this issue.

Conclusions: OCPs and Acne
- Many demonstrate benefit.
- They can be used safely in conjunction with most oral antibiotics.
- They do increase the risk of venous thromboembolism.

MINI-SYMPOSIUM: CUTANEOUS ONCOLOGY & IMMUNOLOGY

Skin Changes After Transplantation: The Rashes
Oscar R. Colegio, MD, PhD

Introduction. The transplant recipient’s notably increased risk for developing squamous cell carcinomas (SCC) as a consequence of immunosuppression is well recognized, but “the most common complaint of patients is actually the rashes that develop secondary to their immunosuppressive drugs,” Dr. Colegio observed. He identified these drugs, described the various cutaneous conditions they cause and the timeline in which they develop, and suggested available treatment approaches.

Immunosuppression. Colegio described the complex molecular pathway leading to clonal memory T-cell proliferation and response that—without suppression—would reject transplanted tissue. This pathway begins when antigen-presenting cells (APC) present the graft antigen to the receptors of naïve T cells while partner molecules on the APC and T cell connect to identify the antigen as foreign, not host. Critical steps along the way to clonal T-cell proliferation include calcineurin activation and IL-2 secretion. Corticosteroids, ie, prednisone, inhibit IL-2 expression. Calcineurin inhibitors—initially cyclosporine, now more commonly tacrolimus—intervene higher upstream. Traditional antiproliferative agents—azathioprine historically, now mycophenolate mofetil more commonly—interfere directly with T-cell cycle progression. Everolimus and sirolimus impair cell cycle progression via mTOR inhibition and are gaining recognition in the transplant community.

Chronology. In the induction of immunosuppression just before transplant, a patient’s T cells are eliminated by the anti-lymphocyte antibodies in antithymocyte globulin (ATG). This can produce serum sickness ~7 days after infusion. The post-transplant period extends from 1 week to several years. Steroid-induced acne erupts abruptly, predominating on the torso, ~1 week–1 month after beginning high-dose steroids. Topical retinoids are effective therapies; this problem tends to resolve when systemic corticosteroids are tapered. Sirolimus-induced acne—resembling the acne induced by EGFR inhibitors—erupts at ~1 month and predominates on the face. Standard treatments may be helpful. Acute GVHD (graft-vs-host disease) often occurs within 2 days–6 weeks of transplant and is fatal in 75%–90% of cases because the disease destroys the bone marrow and patients succumb to infections. At ~3 months, prednisone-induced Cushing’s syndrome appears (which improves during taper) as well as cyclosporine-induced gingival enlargement (fastidious oral hygiene is imperative). At ~5 months sirolimus-induced lymphedema emerges, a potentially severe and possibly irreversible impairment. Drug cessation is the common solution. Hair changes appear between 6 months–1 year, both cyclosporine-induced abnormal growth (hirsutism and hypertrichosis) and tacrolimus-induced alopecia. Significant infections can develop at any time after transplantation—trichodysplasia spinulosa (a rare skin disease associated with a polyoma virus) and widespread local infections, ie, eczema herpeticum and tinea versicolor—as well as Kaposi’s sarcoma from HHV8 infection. Human papilloma virus becomes common at 3 years, as well as cyclosporine-induced sebaceous hyperplasia (a condition that is quite a challenge to treat).

(Continued on page 15)
Significant AK lesion reduction at 1, 2, and 4 weeks

![Graph showing percent reduction in lesion count over time for Weiss Study and Jorizzo Study]

*P<.001 vs vehicle.

Results from two Phase 3 vehicle-controlled, randomized, double-blind, multicenter studies of patients (N=384) with actinic keratoses. Secondary endpoint of percent reduction (least squares mean) in AK lesions at 1, 2 and 4 weeks compared active to vehicle.

### Significant mean reduction in the number of AK lesions with 1 week of treatment compared to vehicle

- Flexibility to prescribe for as little as 1 week or as long as 4 weeks, depending on tolerability and treatment goals.

Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

### Important Safety Information

Carac is contraindicated in women who are nursing, pregnant or may become pregnant as fluorouracil may cause fetal harm.

Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.

Rarely, unexpected, systemic toxicity (e.g., stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase “DPD” activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills.

Carac should be discontinued if severe abdominal pain, bloody diarrhea, vomiting, fever, or chills develop when using the product.

Application of Carac to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

In clinical trials, the most common drug-related adverse events were application site reactions (94.6%), which included: erythema, dryness, burning, erosion, pain, and edema, and eye irritation (5.4%).

Patients using Carac should avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.

### Please see brief summary of full Prescribing Information on adjacent page.

**References:**

2. Jorizzo J, Stewart D, Bucko A, et al. Randomized trial evaluating a new 0.5% fluorouracil formulation demonstrates efficacy after 1-, 2-, or 4-week treatment in patients with actinic keratosis. Cutis. 2002;70:335-339.

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Carcin 

Rx Only 

BRIEF SUMMARY

IMPORTANT NOTE: This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing. This summary has been prepared by deleting information from the complete prescribing information such as certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing for the first time.

FOR TOPICAL DERMATOLOGICAL USE ONLY (NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE)

INDICATIONS AND USAGE

Carcin is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

CONTRAINDICATIONS

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. No adequate and well-controlled studies have been conducted in pregnant women with either topical or parenteral forms of fluorouracil. One birth defect (ventricular septal defect) and cases of micromegence have been reported when fluorouracil was applied to mucous membrane areas. Multiple birth defects have been reported in the fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Carcin. Fluorouracil, the active ingredient, has been shown to be teratogenic in mice, rats and hamsters when administrated parenterally at doses greater than or equal to 10, 15 and 33 mg/kg/day, respectively, 4K, 11K and 20K, respectively, the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA). Fluorouracil was administered during the period of organogenesis for each species. Embryotoxic effects occurred in monkeys at MRHD based on body surface area (BSA) during the period of organogenesis. Carcin should not be used in patients with dihydroxypropylidene dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catalyzed by the enzyme dihydroxypropylidene dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytocidal activity and potential teratogenicity. Carcin is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive. Patients should discontinue therapy with Carcin if symptoms of DPD enzyme deficiency develop. Rarely, ulcerated, systemic toxicity (e.g., stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parental administration of fluorouracil has been attributed to deficiency of dihydroxypropylidene dehydrogenase (DPD) activity. One case of life threatening systemic toxicity has been reported with the topical use of fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

Adverse reactions to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

PRECAUTIONS

General

There is a possibility of increased absorption through ulcerated or inflamed skin.

Information for the Patient

Patients using Carcin should receive the following information and instructions:
1. This medication is to be used as directed.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. It is for external use only.
4. Avoid contact with the eyes, eyelids, nostrils, and mouth.
5. Cleanse affected area and wait 10 minutes before applying Carcin.
6. Wash hands immediately after applying Carcin.
7. Avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.
8. Most patients with Carcin show skin reactions where the medicine is used. These reactions include redness, dryness, burning, pain, erosion (of the upper layer of skin), and swelling. Initiation of the application site may persist for two or more weeks after therapy is discontinued. Treated areas may be unsightly during and after therapy.
9. If you develop abdominal pain, bloody diarrhea, vomiting, fever, or chills while on Carcin therapy, stop the medication and contact your physician and/or pharmacist.
10. Report all adverse effects to the physician and/or pharmacist.

Laboratory Tests

To rule out the presence of a frank neoplasm, a biopsy may be considered for those areas failing to respond to treatment or recurring after treatment.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Carcin, fluorouracil, have shown positive effects in in vitro and in vivo tests for mutagenicity and an impairment of fertility in in vivo animal studies. Fluorouracil produced morphological transformation of cells in in vitro cell transformation assays. Morphological transformation was also produced in an in vitro assay by a metabolite of fluorouracil, and the transformed cells produced multiple colonies. The transformed colonies were shown to be separated into transformed and untransformed cells. Fluorouracil has been shown to exert mutagenic activity in yeast cells, Bacillus subtilis, and Drosophila assays. In addition, fluorouracil has produced chromosomal damage at concentrations of 1.0 and 2.0 mg/ mL in an in vitro assay using human lymphocytes. Positive results were obtained in in vivo micronucleus assays in rats and mice following intraperitoneal administration. Some patients receiving cumulative doses of 0.2 to 1.0 g of fluorouracil parenterally have shown an increase in numerical and structural aberrations in peripheral blood lymphocytes.

Fluorouracil has been shown to impair fertility after parental administration in rats. Fluorouracil administered at intraperitoneal doses of 125 and 250 mg/kg has been shown to induce chromosomal aberrations and changes in organ weight in rats. Maternal oral administration of fluorouracil was reported to kill differentiated spermatogonia and spermatocytes at a dose of 500 mg/kg and produce abnormalities in spermatids at 50 mg/kg.

Pediatric Use

Actinic keratosis is not a condition seen within the pediatric population, except in association with rare genetic diseases. Carcin should not be used in children. The safety and effectiveness of Carcin have not been established in patients less than 18 years old.

Geriatric Use

No significant differences in safety and efficacy measures were demonstrated in patients age 65 and older compared to all other patients.

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS

Nursing Women

It is not known whether fluorouracil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when administering this drug to a nursing woman.

ADVERSE REACTIONS

The following were adverse events considered to be drug-related and occurring with a frequency of ≥1% with Carcin: application site reaction (94.6%), and eye irritation (5.4%). The signs and symptoms of facial irritation are application site reactions are presented below.

Summary of Facial Irritation Signs and Symptoms - Pooled Phase 3 Studies

<table>
<thead>
<tr>
<th>Clinical Sign or Symptom</th>
<th>Active One Week N=85</th>
<th>Active Two Weeks N=87</th>
<th>Active Four Weeks N=85</th>
<th>All Active Treatments N=257</th>
<th>Vehicle N=127</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>76 (89.4)</td>
<td>92 (98.9)</td>
<td>203 (94.3)</td>
<td>75 (59.8)</td>
<td></td>
</tr>
<tr>
<td>Dryness</td>
<td>59 (69.4)</td>
<td>76 (87.4)</td>
<td>219 (82.4)</td>
<td>51 (40.7)</td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>51 (60.0)</td>
<td>70 (80.5)</td>
<td>212 (79.5)</td>
<td>52 (40.7)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>26 (30.6)</td>
<td>34 (39.1)</td>
<td>52 (21.2)</td>
<td>112 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>12 (14.1)</td>
<td>28 (32.2)</td>
<td>51 (20.0)</td>
<td>91 (35.4)</td>
<td></td>
</tr>
</tbody>
</table>

During clinical trials, irritation generally began on day 4 and persisted for the remainder of treatment. Seventy-four percent of patients at the last visit was slightly below baseline for the vehicle group, mild to moderate for the 1 week active treatment group, and moderate for the 2 and 4 week active treatment groups. Mean severity declined rapidly for each active group after completion of treatment and was below baseline for each group at the week 2 post-treatment follow-up visit. Thirty-six percent (12% of those treated with Carcin in the Phase 3 clinical studies) discontinued study treatment early due to facial irritation. Except for three patients, discontinuation of treatment occurred on or after day 11 of treatment. Eye irritation adverse events, described as mild to moderate in intensity, were characterized as burning, watering sensitivity, stinging and itching. These adverse events occurred across all treatment arms in one of the Phase 3 studies.

Adverse Reactions Experienced by Body System

In the Phase 3 studies, no serious adverse event was considered related to study drug. A total of five patients, three in the active treatment groups and two in the vehicle group, experienced at least one serious adverse event. Three patients died as a result of adverse event(s) considered unrelated to study drug (stomach cancer, myocardial infarction and cardiac failure).

Post-treatment clinical laboratory tests other than pregnancy tests were not performed during the Phase 3 clinical studies. Laboratory tests were performed during the Phase 2 study of 104 patients and 21 patients in a Phase 1 study. No abnormal serum chemistry, hematology, or urinalysis results in these studies were considered clinically significant.

DOSAGE AND ADMINISTRATION

Carcin cream should be applied once a day to the skin where actinic keratosis lesions appear, using enough to cover the entire area with a thin film. Carcin cream should not be applied near the eyes, nostrils, or mouth. Carcin cream should be applied ten minutes after thoroughly washing, rinsing, and drying the entire area. The cream may be applied using the fingertips. Immediately after application, the skin should not be touched. Washed Carcin should be applied up to 4 weeks as tolerated. Continued treatment up to 4 weeks results in greater lesion reduction. Local irritation is not markedly increased by extending treatment from 2 to 4 weeks, and is generally resolved within 2 weeks of cessation of treatment.

OVERDOSE

Ordinarily, topical overdose will not cause acute problems. If Carcin is accidentally ingested, induce emesis and gastric lavage. Administer symptomatic and supportive care as needed. If contact is made with the eye, flush with copious amounts of water.

HOW SUPPLIED


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Genetic Tumor Syndromes: New Insights and Therapeutic Advances
Julie V. Schaffer, MD

Introduction. Dr. Schaffer provided an overview of genetic tumor syndromes related to two important signaling pathways—RAS/mitogen-activated protein kinase (MAPK) and PI3K/PTEN/Akt/mTOR—that influence cell proliferation.

RASopathies. The classic RAS pathway genodermatosis is neurofibromatosis type 1 (NF1). Multiple café-au-lait macules and (in ~25% of patients) plexiform neurofibromas appear early in life, whereas smaller cutaneous neurofibromas typically begin to develop around puberty. In addition to a heterozygous germline mutation in the \( NF1 \) tumor suppressor gene, which produces the neurofibromin protein that normally negatively regulates RAS signaling, a “second hit” \( NF1 \) mutation in affected tissues results in a hyperactive pathway. NF1-deficient Schwann cells secrete Kit ligand that stimulates mast cells, which facilitate neurofibroma development. The Kit inhibitor imatinib and other kinase inhibitors are promising treatments for problematic plexiform neurofibromas. Another tumor suppressor gene, \( SPRED1 \), affects neurofibromin function and inhibits RAS signaling. \( SPRED1 \) defects produce the recently recognized NF1-like Legius syndrome.

Schaffer described several other conditions caused by germline mutations that activate RAS/MAPK pathway proteins. She emphasized these disorders’ shared phenotypic features, including pigmented lesions and acanthosis nigricans. She noted that most sebaceous nevi and ~one-third of epidermal nevi are caused by mosaic activating RAS mutations. Furthermore, mosaicism for an \( HRAS \) mutation underlies the concurrence of speckled lentiginous nevus (the melanocytes are affected) with nevus sebaceus (the keratinocytes are affected) in phacomatosis pigmentokeratotica, a form of “twin spotting.”

PTEN/AKT/mTOR Defects. Bannayan-Riley-Ruvalcaba syndrome, with features (eg, vascular anomalies) appearing early in life, and Cowden disease, with adult-onset skin findings (eg, trichilemmomas) and increased cancer risks, represent two temporally defined ends of the phenotypic spectrum of PTEN mutations. Schaffer described overlapping features—eg, epidermal nevi, vascular malformations—of “Proteus-like syndrome” due to an early “second hit” in PTEN, true Proteus syndrome caused by mosaic \( AKT1 \) mutations, and megalencephaly-capillary malformation and CLOVES syndromes resulting from mosaic \( PIK3CA \) mutations. These clinical similarities are not surprising considering the shared PI3K/PTEN/Akt/mTOR pathway activation. Schaffer concluded by discussing tuberous sclerosis (TS), a genodermatosis caused by loss-of-function mutations affecting tuberin or hamartin, proteins that function downstream in this pathway and normally restrain mTOR activity. Systemic sirolimus (rapamycin) has proven helpful for internal manifestations of TS, and its topical use causes regression of facial angiofibromas in TS patients.

RAS Pathway Mutations Involved in Genetic Tumor Syndromes

RASopathies: Shared Phenotypic Features

- Curly/woolly/loose anagen hair
- Keratosis pilaris (atrophicans) [CFC, Noonan]
- Acanthosis nigricans
- Lentigines, CALM, melanocytic nevi


Costello Syndrome: HRAS

- Curly hair, premature hair loss
- Loose acral skin with deep creases
- Acanthosis nigricans
- Periorificial papillomas
- Nevi, lentigines
Cutaneous T-Cell Lymphoma: Evolving Diagnostics and Therapeutics

Kevin D. Cooper, MD

Introduction. Dr. Cooper reviewed current cutaneous T-cell lymphoma (CTCL) classification, diagnosis, evaluation, TNMB classification, and treatments, amplified with his extensive experience and salient insights.

Classification. Mycosis fungoides represents roughly half of all primary CTCLs and the majority of typical forms. Five-year survival is excellent, with normal life expectancy for stage I disease. Follicular MF, CD30+ large cell lymphoma, and lymphomatoid papulosis also have excellent 5-year survival rates. Rates plummet for CD30– small/medium cell peripheral T-cell lymphoma (PTCL), CD30– large cell PTCL, CD30– NK/T-cell lymphoma, and Sezary syndrome. Cooper also discussed challenges of CD8+ lymphomas, periocular MF, and hypopigmented MF.

Diagnosis. Because of CTCL’s pronounced morphologic variation, “the differential diagnosis comes up more than we would like.” Lesional morphologic and histologic differences in part reflect the type of malignant T cell, eg, some cytotoxic resident memory T cells may produce more lesions with a somewhat lichenoid interface histology; Th2-producing CD4 T cells may create more spongiotic lesions. Diagnosis requires assembling clinico-pathologic correlation of consistent lesion morphology and distribution, histologic findings, immunophenotypic results, and clonality determination by molecular testing (determined by T-cell receptor–TCR–gene rearrangement or over-representation of T cells with a distinctive TCR chain) or by flow cytometry of a lesion or blood sample. Immunohistochemistry identifying the predominance of CD2+, CD3+, or CD4+ T cells, combined with the loss of such normal T-cell markers as CD45RO, CD7, CD3 or the presence of numerous CD30+ T cells, can be definitive. Once diagnosis is confirmed, Cooper described the factors determining the workup he orders, then explained TNMB classification criteria.

Treatments. Cooper uses skin-directed therapies for early-stage patients. In unileisonal MF, where there is a chance for cure, he bypasses topical steroids for local radiation, aggressive narrow-band UVB, or excimer laser. He referred to their published data showing prolonged complete responses with radiation and specified his treatment protocol. For stage IA (limited patch/plaque)/IB disease, skin-directed therapies (eg, phototherapy and topical nitrogen mustard or bexarotene) are favored initially, followed by systemic treatments such as bexarotene, IFN-α, and vorinostat alone or with the skin-directed therapies. Progressive or more advanced disease can be treated with total body skin electron beam therapy or parenteral agents (eg, rhomidepsin or pralatrexate, or brentuximab for CD30+ disease). Multiagent chemotherapy is reserved for severely refractory patients because of its panimmunosuppressive impact. Cooper discussed “how to integrate topical and systemic treatments, and where to use them at various stages of the disease.” For Sezary syndrome, for example, “extracorporeal photopheresis and vorinostat are my go-to therapies, alone or in combination. Next in line would be IFN-α.”

Classification of Primary Cutaneous CTCLs

<table>
<thead>
<tr>
<th>Classification</th>
<th>Frequency</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
<td>50%</td>
<td>89%</td>
</tr>
<tr>
<td>Follicular MF</td>
<td>5%</td>
<td>75%</td>
</tr>
<tr>
<td>CD30+ large-cell (ALCL)</td>
<td>12%</td>
<td>93%</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>18%</td>
<td>100%</td>
</tr>
<tr>
<td>CD30– small/medium-cell PTCL</td>
<td>2%</td>
<td>62%</td>
</tr>
<tr>
<td>CD30– large-cell PTCL</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>CD30– NK/T-cell lymphoma</td>
<td>3%</td>
<td>11%</td>
</tr>
</tbody>
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Diagnosis of CTCL

- Diagnosis is based on a combination of
  - Clinical
  - Histologic
  - Immunophenotypic criteria
    - CD3+, CD2+, CD4/8
    - Marker loss: CD45RO, CD7
  - Clonality
    - T-Cell Receptor gene rearrangement study
    - Anti-T-Cell Receptor V beta subtype
    - Tissue or blood flow cytometry
- Points

CTCL Workup

- Labs:
  - CBC, blood chemistry panel, LDH, cytology, immunophenotyping
- Lymph node biopsies if clinically significant, accessible adenopathy
- If >10% body surface area, CT scans of chest and abdomen
- Blood flow cytometry if high body surface area or erythrodermic
- Bone marrow sampling if high suspicion from clinical or lab data
- Organ biopsy if high clinical suspicion

Special Gifts for Dermatologic Research

Tribute and Honoraria contributions are an effective, but often overlooked, way to support research through the Dermatology Foundation.

Tribute Contributions: A meaningful way to increase the DF’s capacity for funding deserving research projects is by memorializing or honoring someone important to you—a family, special friend, or mentor.

Honoraria: A unique way to make your member contribution this year is to arrange to have honoraria paid directly to the DF.

All contributions to the DF are deeply appreciated and help maintain the momentum of progress in the specialty. For more information on contributing gifts of this kind, contact the DF office at 847.328.2256.
The Dermatology Foundation is grateful to the following corporations for their generous contributions last year. Their support furthers the DF’s mission to develop and retain tomorrow’s leaders in the specialty and advance patient care.

**Cornerstone Benefactor ($500,000)**

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![ Valeant Pharmaceuticals International Logo]

**Gold Benefactor ($100,000)**

The Allergan Foundation  
Merz  
SkinMedica, Inc., an Allergan Company

**Silver Benefactor ($50,000)**

Avon Products, Inc.  
Obagi Medical Products  
Stiefel, a GSK company
The outstanding impact of the Dermatology Foundation’s Research Awards Program is nationally recognized. It provides essential funding opportunities for effectively advancing the early research efforts and careers of talented new physician-scientists and investigators. This support from the Foundation enables the experience and initial data required to be successfully competitive for highly prized NIH grants and other external funding. These early-career awards are now more critical than ever with the current mandatory cuts in federal grants.

*The DF’s program offers multi-year career development awards and one-year fellowships and grants that support research in all areas of modern dermatology and cutaneous biology.* Award recipients are those who have the capacity and desire to further the future of dermatology and patient care. These awards are made possible by the Foundation’s many members and industry supporters.

### Career Development Awards (CDAs)

The nine categories of CDAs are designed to enable physician-scientists and investigators to transition from fellowship to established researcher. These highly competitive and effective awards are reserved for those who show the greatest potential to contribute to the specialty. Each award provides an annual stipend of $55,000 for up to three years of support.

- **Physician Scientist CDA**
- **Clinical CDA in Dermatologic Surgery**
- **Pediatric Dermatology CDA**
- **Dermatopathology Research CDA**
- **Clinical CDA in Health Care Policy/Public Health**
- **Medical Dermatology CDA**
- **Science of Human Appearance CDA**
- **Women’s Health CDA**
- **Basic Research CDA**

### Fellowships

Two one-year fellowships are offered—the Dermatologist Investigator Research Fellowship and the Fellowship in Pediatric Dermatology. They provide salary stipends of $30,000 and $45,000, respectively.

### Research Grants

These one-year grants offer $20,000 in seed money for research projects in a variety of concentrations, including patient-directed investigation, basic dermatologic research, and dermatopathology. This year, special funding is also available in the basic research grant category for dermatopharmacology projects.

### Program Development Grant

This unique grant provides $10,000 to further the scientific infrastructure of an existing dermatology division or department that has not successfully competed for DF funding within the last five years.

**APPLY NOW!**

Research award proposals are being accepted through October 15th for the funding year beginning July 1, 2014.

Visit [www.dermatologyfoundation.org/rap](http://www.dermatologyfoundation.org/rap) for everything you need:

- detailed award descriptions, eligibility criteria, application instructions, and downloadable forms.

Questions are welcomed by the DF staff:

847.328.2256 or dfrap@dermatologyfoundation.org

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CLINICAL SYMPOSIA 2013 FACULTY
Proceedings—Part II

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The DF is pleased to recognize Unilever for their educational grant of $300,000 supporting the 2013 DF Clinical Symposia Resident Program.

2013 DF Clinical Symposia Faculty Disclosures (Part II)

Why Are You a Leader?

The DF’s Leaders Society is an effective way to give back to the specialty, with an impact that lasts well into the future. A new Young Leader—a dermatologist who chooses to begin this commitment within 5 years after residency—shares his decision to join his colleagues in leadership giving.

Brock A. Andersen, MD: “The DF is Relevant and Meaningful”

“Dermatology is a wonderful field, and we are lucky to be in it,” says Dr. Andersen, who is in his first year of private practice in rural Idaho. He notes the personal satisfaction of seeing patients “from start to finish, including biopsy and surgery,” and also points to dermatology’s historical role in a number of medical advances.

He believes strongly that “we all need to do our part to make sure that dermatology continues to be a significant contributor to general medical care, and to keep our specialty advancing. This translates to carrying out needed research, or enabling others to do it.”

When Dr. Andersen was completing his residency in 2012, he knew it would be a long while before he could engage in research himself and so he began looking for “a meaningful group to support.” He found it in his first direct exposure to the Dermatology Foundation.

“I attended the DF’s Clinical Symposia last year, and that’s where I made my decision. I learned about the research projects the Foundation funds and the research careers they are successful in launching. This is the kind of effective research that is really going to better people’s lives and better our practices. I hope to do my own research in the future. But until then, being a Leaders Society member allows me to be part of something that is at the forefront of meaningful dermatology research.”