AOCD 2012 Annual Meeting

The second annual University of Pennsylvania Symposium, a presentation by Dan Siegel, M.D., FAAD, the President of the American Academy of Dermatology (AAD), and many interesting and informative lectures on such topics as novel pediatric dermatology treatments, cosmeceuticals, and body art are just some of the highlights from the 2012 Annual Meeting held this past October in sunny San Diego. The following are excerpts from the presentations.

AAD Update

Dr. Siegel highlighted strategic initiatives the AAD has in place to help members navigate the rapidly changing landscape related to practice, policy, and patient care.

Regarding patient care, the AAD has recalibrated its continuing medical education (CME) offerings to align with the changing accreditation requirements of the Accreditation Council for Continuing Medical Education and the American Board of Dermatology (ABD) Maintenance of Certification program. The Council on Education is focused on providing meaningful outcomes-based CME that enables physicians to immediately implement what they’ve learned in their practices to enhance patient care, he said.

The Academy is committed to developing evidence-based guidelines to help members satisfy requirements by accrediting organizations and the government to measure and demonstrate quality patient care. Reflecting the AAD’s belief that measures should be based on guidelines developed by dermatologists, as opposed to non-experts, the Academy has brought together dermatologists to develop such guidelines. Dr. Siegel said. Guidelines are currently available for psoriasis, acne, and melanoma. This year, guidelines will transition from consensus to evidence-based guidelines for atopic dermatitis (AD) and anesthesia use in the office.

Similarly, the AAD moved quickly to develop Appropriate Use Criteria (AUC) for Mohs to preserve the specialty’s ability to use the procedure for patients where the benefit is most widely accepted. The AUC document, which has been published online and in journals, is expected to be used to combat denial of coverage for Mohs surgery by carriers. “If its use is determined to be appropriate based on the AUC, there’s a high likelihood that the insurance companies will pay for it,” he stated.

For quality reporting purposes, the AAD has developed three melanoma measures available on the Physician Quality Reporting System. The newest one is the prevention of overutilization of imaging for stage 1 melanoma. The Academy is collaborating with other organizations to develop a set of measures for AD, which will be incorporated into Maintenance of Certification activities.

With regard to public educational efforts, Dr. Siegel reviewed SPOT Skin Cancer”, the Academy’s newest, public awareness initiative about skin cancer prevention and detection. In addition to skin cancer facts and tips on skin protection, the website includes opportunities for visitors to share their stories, explain how to get involved, and connect with others. The focus is on the positive actions people can take to protect themselves from skin cancer, including seeing a board-certified dermatologist when appropriate.

Raising public awareness as accountable care organizations move forward is also critical. We must demonstrate the need to see a board-certified dermatologist. “It’s not that we want a
deluge of patients,” he said, “but if we don’t keep in the public eye, we’ll get marginalized.” Dermatologists must get involved in the medical community-at-large, as well. “If you’re not considered an important player, you may be marginalized,” Dr. Siegel stressed. It’s also important to go to Washington to be an influential voice.

Next, Dr. Siegel mentioned recent successes that resulted from American Academy of Dermatology Association, or AADA, advocacy, often in partnership with other national and state dermatologic and patient societies. They included the Food and Drug Administration (FDA) announcing sunscreen regulations; the indoor tanning tax being upheld and the cosmetic tax being kept off the table; the Stark in-office ancillary exception being kept in place; the under-18 indoor tanning bans being secured in California and Vermont; onerous state legislation being killed in Louisiana, New Jersey, and other states and; the reversal of modifier 25 reductions in Kentucky and Indiana. The AAD launched the Dermatology Advocate enewsletter and the Recovery Audit Contractor, or RAC, Audit Survival Toolkit. Meanwhile, the Relative Value Scale Update Committee, or RUC team, continues to effectively work to maintain fair valuation of dermatology services, he said.

Opportunities at the state level include opposing onerous office-based surgery requirements, promoting patient safety in medical specialties, and advocating for truth and transparency in healthcare advertising. Dermatologists must engage at the state level by responding to policy proposals affecting the practice of medicine and initiating a dialogue with all stakeholders to find commonalities and opportunities to work together, Dr. Siegel noted.

Healthcare reform is a tsunami, he stated. “It’s not a question of if it will hit, but rather when.” After providing an update on Congress’ effort, or lack thereof, to reduce the federal deficit and address Medicare’s sustainable growth rate, Dr. Siegel urged audience members to contribute to SkinPAC, the AADA’s political action committee.

“The Academy is actively engaged on a wide range of important issues and well positioned to meet the challenges they pose. We have achieved some significant success on many of them and will continue our work in Washington, with the media, and with other stakeholders to benefit our members and patients,” he concluded.

**Rheumatic Skin Disease**

Next, panel members convened for the second annual University of Pennsylvania Symposium. They included Victoria Werth, M.D.; Brian Kim, M.D.; Emily Chu, M.D., PhD; and Michael Ming, D.D., MSCE; all of whom are from the University of Pennsylvania Health System.

In her presentation entitled *Rheumatic Skin Disease*, Dr. Werth reviewed the criteria for systemic lupus erythematosus (SLE) published by the American College of Rheumatology. Despite some criticisms, nobody has been able to improve upon the criteria. They include malar or discoid rash; photosensitivity; oral ulcers; arthritis; serositis; and renal, neurological, immunological, or hemotologic disorder. Because the college’s classification criteria include somewhat overlapping dermatologic criteria (i.e., butterfly rash, discoid lupus, photosensitivity, and oral ulcers) it raises issues of case definition for cutaneous lupus erythematosus (CLE) versus SLE, she said. Patients can be classified as having SLE with only skin manifestations or without significant systemic disease.

Patients with CLE have a severely impaired quality of life, especially with respect to emotional well-being, Dr. Werth noted. Studies have shown that they have a worse quality of life than those with other common dermatologic conditions, and similar or worse scores than patients with hypertension, type II diabetes, and recent heart attack.

Skin lesions in patients with CLE could be LE-specific or LE-nonspecific. “Making the diagnosis isn’t always easy,” she said. Skin biopsy shows LE-specific histology. A diagnosis of LE can be confirmed regardless of whether ACR criteria for SLE are present. LE-nonspecific CLE is not histopathologically distinct for LE and/or may be seen as a feature of another disease process. LE skin lesions come in three subsets: chronic, subacute, and acute CLE. The types of skin lesions in each group are clinically distinct; recognizing the specific subsets helps to determine the likelihood of underlying systemic lupus, Dr. Werth added.

Chronic CLE is further categorized into localized discoid LE (DLE), generalized DLE, hypertrophic LE, lupus panniculitis, tumid LE, and chilblain LE. Patients with DLE, which is the most common form of chronic CLE, will need to be followed with annual labs and reassured that it is unlikely they will get SLE, she said. The same is true for patients with tumid LE. Only 19% of patients with CLE progress to SLE.

The diagnosis of CLE is usually made by clinical examination with histopathology used to confirm it. Very often, histopathology is sufficient to confirm the diagnosis, but Dr. Werth also may use direct immunofluorescence. The latter is especially helpful for diagnosing lupus panniculitis and subacute CLE. The additional testing is helpful when the lesions are hard to distinguish. She also may look for lupus-specific antibodies, which may or may not be present. If Dr. Werth suspects SLE, she will check for organ involvement by way of urinalysis, kidney function, and...
blood count. Patients with skin-only disease should be checked periodically for systemic disease.

Inflammatory skin disease has been found in up to 70% of patients with SLE. LE-nonspecific lesions usually occur in the active phase of the disease. Those with LE-nonspecific lesions tend to have increased disease activity compared with those who have only LE-specific lesions and those with both types of lesions.

The prognostic significance of CLE is as follows: Patients with skin disease tend to have only localized DLE, hypertrophic LE, LE panniculitis, and tumid LE. However, patients with generalized DLE and SCLE fall somewhere in the middle. Patients with systemic disease tend to have acute CLE and LE-nonspecific skin disease.

Be aware that the number of medications causing SLE and CLE is ever expanding, Dr. Werth said. Among them are thiazide diuretics, calcium channel blockers, antifungals, beta blockers, nonsteroidal anti-inflammatory agents (NSAIDs), antihistamines, chemotherapy drugs, angiotensin converting enzyme inhibitors, gastrointestinal acid inhibitors, tumor necrosis factor-alpha, or TNF-α inhibitors, and platelet inhibitors. If the patients discontinue the drug, they do better, but it's not easy to get off of these, she added.

One of the challenges in managing patients with CLE is the development of novel therapeutic agents, Dr. Werth said. One reason for this is the difficulty in designing clinical trials for a disease that is so heterogeneous in nature. Consequently, the FDA recommended focusing on organ-specific therapies. In 2005, an organ-specific index of disease activity—the Cutaneous Lupus Erythematosus Disease Area and Severity Index or CLASI—was developed. Since then, it has been validated by many studies. The incidence of refractory disease is 10%. Patients with generalized DLE are more refractory to current therapies than those with localized DLE or SCLE. Additionally, smokers are more refractory to all treatments.

Preventive therapies include avoiding heat, sunlight and artificial ultraviolet light, and using sunscreens with an SPF of greater than 70, she stated. Treatment options include topical steroids, topical nonsteroidal T-cell inhibitors, and intralesional steroids. She uses antimalarials, specifically hydroxychloroquine, chloroquine, and quinacrine, which can be switched out if one doesn’t result in any improvement. Prescribing combination antimalarials has been shown to be efficacious. If antimalarials don’t work, consider diaminodiphenylsulfone (Dapsone), retinoids, thalidomide, methotrexate (MTX), or corticosteroids, Dr. Werth advised. Steroids should not be used for skin predominant disease. Thalidomide works rapidly with a full clinical response in two to three months, but it has numerous, serious side effects. Seventy-five percent of patients with refractory disease respond to antimalarials.

Belimumab, the first drug in more than 50 years approved for the treatment of SLE, was approved in 2010. Its affects are fairly modest, she said. Anti-cytokines, T-cell and B-cell directed therapy, chemokine antagonists, and anti-adhesion molecules are also being looked at. Thalidomide analogues may prove as effective as thalidomide without its toxicity.

Dr. Werth also discussed dermatomyositis (DM), which has characteristic cutaneous manifestations and proximal muscle weakness and is frequently misdiagnosed as lupus. “We have a role in getting these patients the correct diagnosis,” she said. Signs include violaceous and malar erythema, alopecia, mechanic’s hands, cutaneous vasculitis, and deep ulcers. Many dermatology patients do not have the muscle disease component that is required for a diagnosis of DM; consequently they fall through the cracks. Rheumatologists see different patients than dermatologists do, she said. The latter cases are referred to as amyopathic DM, which are confused with SLE. These patients must have a work-up to determine if they have muscle involvement. In addition, they should be evaluated for systemic involvement, especially of the pulmonary system, and for the possibility of an accompanying malignancy. The risk of malignancy is highest in the first three years of diagnosis, Dr. Werth noted. Twenty-three percent of patients with DM have interstitial lung disease, which is treatable and reversible if caught early. One of the challenges to diagnosing and treating DM is that no data exists for how to best approach it. Treatment for DM should be based on underlying muscle or pulmonary disease. In addition to sun avoidance and the use of sunscreens and topical steroids, antimalarials are the first line of therapy. If those don’t work, try immuno suppressives, glucocorticoids, and thalidomide. Intravenous immunoglobulin is a very expensive and time consuming rescue drug. Experimental therapies include B-cell directed therapies and cytokine inhibitors. However, more research is needed.
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AD Update

The three assumptions with which Dr. Kim began his presentation were as follows: Everyone knows how to diagnose AD, there will be no discussion about conventional/existing therapies, and it is a frustrating disease to treat because conventional therapies are fairly limited.

He reviewed the two primary hypotheses regarding the development of inflammation that leads to AD. The immune dysregulation hypothesis ascertains that primary immunodeficiencies result in an aberration response—an overstimulation of the immune system pathway—in the skin. Specifically, immune dysregulation causes an imbalance in the T-cells, which triggers the production of Th2 cytokines, namely interleukin (IL)-4, IL-5, and IL-13, causing an increase in immunoglobin E from plasma cells and diminished interferon-gamma levels.

The barrier dysfunction hypothesis suggests that patients develop AD as a result of skin barrier defects that allow for the entry of antigens, resulting in the production of inflammatory cytokines. Mutations in filaggrin, which is a key skin barrier protein, may initiate allergic inflammation in the skin and the “atopic march.” Specifically, filaggrin defects are associated with dysregulation of epidermal-derived cytokines (IL-25, IL-33 and thymic stromal lymphopoeitin) that promote allergic inflammation. Finally, novel or previously unrecognized innate cell populations are elicited by epidermal-derived cytokines.

Explaining the role of bacterial colonization on AD, Dr. Kim noted that *Staphylococcus aureus* may enhance allergic inflammation via epidermal cell-derived cytokines, such as thymic stromal lymphopoeitin. *S. aureus* colonization is associated with AD flares and decreased commensal microbial activity. Conversely, commensal bacterial diversity is associated with improved AD.

A current hot topic in the biomedical literature is the role of skin bacteria in AD: pathogens versus commensal organisms. “You have healthy bacteria on skin competing with unhealthy bacteria such as *S. aureus*,” he said. Studies have shown that if commensal bacteria are depleted, it enhances systemic allergic (atopic) inflammation. Additionally, studies suggest that probiotics may help in the treatment of AD. In studies, the use of probiotics reduced gut microbial translocation and improved AD. Following therapy, subjects had a high Th1 and Th2 ratio, which is consistent with findings from a study Dr. Kim conducted. When discussing the role of commensal fungi, he referenced a study looking at the role of Malassezia in AD affecting the head and neck. Because colonization of Malassezia provoked Th2 cytokine response, it is suggested that these patients will benefit from a one- to two-month course of daily itraconazole or ketoconazole followed by long-term weekly treatment. A mouse study demonstrated that candida overgrowth is associated with Th2 cytokine responses in the lung. Thus, the current paradigm of AD continues to evolve.

Newer Drug Reactions

Recently approved targeted therapy medications have a decreased systematic toxicity compared with traditional chemotherapy, stated Dr. Chu, but they also have a high rate (>50%) of cutaneous adverse reactions. “Dermatologists play a role in diagnosing and managing these drug reactions,” she said.

Vismodegib is a synthetic smoothened/SMO inhibitor. It was FDA-approved in January 2012 for the treatment of advanced and metastatic basal cell carcinoma (BCC). Vismodegib blocks hedgehog signaling through direct binding to smoothened proteins, she explained. Studies show a 50% to 60% improvement rate in metastatic tumors. Toxicities, which are reversible, include muscle cramps, hair loss, and loss of taste that leads to weight loss. Vismodegib also has shown promising results in the treatment of Gorlin syndrome. But 54% of patients stop taking the drug because of adverse side effects. One solution being considered is to dose the drug accordingly to limit the side effects, Dr. Chu said.

Ipilimumab, which inhibits CTLA-4, was approved by the FDA for the treatment
of metastatic melanoma in March 2011. As many as 50% of patients have skin toxicity as a result of taking the drug; four percent of which experience severe side effects. Antihistamines may help mild symptoms whereas topical steroids may help relieve moderate symptoms, she said. Other dermatologic side effects include pigmentation changes of the hair and skin as well as vitiligo.

There are a number of different medications that target different points along the same pathway, Dr. Chu stated. These drugs target epidermal growth factor receptors because the latter have control over basic cell functions. They are strongly correlated with malignant behavior and associated with resistance to traditional chemotherapy/radiotherapy.

But the epidermal growth factor receptors inhibitors have a number of side effects; the classic one is acneiform eruption seen in 43% to 85% of patients. Other dermatologic side effects include paronychia, xerosis and pruritus, dermatitis, hyperpigmentation, and telangiectasia. Hair changes include alopecia, trichomegaly, hirsutism, and textural changes. There also are gastrointestinal toxicities.

Sunitinib and Sorafenib are two multikinase inhibitors that result in several dermatologic adverse effects. Sunitinib is used to treat advanced renal cell carcinoma and advanced gastrointestinal stromal tumors. Dermatologic reactions include rash (38%), yellow pigmentation (33%), hair depigmentation (17%), hand-foot skin reaction (14%), and alopecia (12%). Sorafenib is used to treat advanced renal cell cancer and advanced hepatocellular carcinoma. The most common side effects associated with it are facial/scalp erythema/dysesthesias (60%), hand-foot skin reaction (27-50%), alopecia (30%), subungual hemorrhages (30%), and pruritus (19%). Vemurafenib was approved by the FDA in August 2011 for the treatment of unresectable or metastatic melanoma with the BRAF V600E mutation. Between 40% and 60% of melanomas have mutations in the BRAF gene, she said. Few effective therapies for metastatic disease exist; vemurafenib has been shown to improve survival and reduce tumor size. The challenge is that patients develop quick resistance to it, Dr. Chu noted. Dermatitis, lobular panniculitis, and photosensitivity are common dermatologic side effects. Fifteen percent of patients get a rash. Keratoacanthoma (KA)-type squamous cell carcinomas (SCCs) or KAs are experienced by 15% to 30% of patients.

It is believed that RAF inhibitor therapy leads to the development of SCCs, she explained. They block MAPK signaling in cells with the V600E mutation, but paradoxical activation of the pathway is observed in cells harboring wild type BRAF. Tumors develop in the setting of paradoxical activation of the MAPK pathway by RAF inhibitors and RAS activation mutations. A recent study found that RAS mutations are associated with the development of SCCs in patients treated with RAF inhibitors. However, the development of SCCs and KAs may be avoided by using combination therapy of BRAF and MEK inhibitors, Dr. Chu said. One study showed that SCCs did not develop in any of the 45 patients treated with combination BRAF and MEK inhibitor therapy.

The use of MEK inhibitor—Selumetinib—is associated with the following cutaneous side effects: papulopustular rash, xerosis, pruritis, and telangiectasias, among others. As these relatively new drugs are on the market longer and new ones are developed, drug reactions will continue to occur, she concluded.

Melanoma Issues

Dr. Ming addressed five clinical dilemmas in the treatment of melanoma.

The first dilemma is how to improve compliance with patient self-examination, he said, adding, “I want every patient to look at his or her own skin.” Even patients at high risk of developing melanoma don’t routinely examine their own skin. Studies show that a low percentage of patients routinely check their skin or undergo screenings. But there is indirect evidence that it is beneficial, Dr. Ming noted. Most melanomas are found by patients, spouses, or significant others. Factors associated with self-examination include being female and older as well as having a higher education and socioeconomic status. Other factors include having a baseline photo for comparison use, a partner who can help, and been told by a physician to do it. “I heavily stress self-examination in patients with a history of melanoma,” he said. "Most patients who don’t have melanoma won’t spend the time.” Dr. Ming helps patients formulate a plan, making them more likely to follow through with self-examination. For example, if the patient isn’t living with anyone who can help, he suggests that they purchase a wall mirror.

The second dilemma is whether or not to advise patients to get genetic testing for melanoma. This is a complicated situation because there are different melanoma susceptibility genes. A match to CDKN2A, which is the gene most often discussed, leads to increased risk of melanoma. But that is true for only five percent of all melanomas, 10% to 15% of multiple primary melanoma patients, and between 20% and 40% of patients with three or more family members with melanoma. “It’s a high penetrance game, but it’s multifactorial,” he stated. Only some patients with a match to CDKN2A are susceptible to developing pancreatic cancer. Moreover, negative results are hard to interpret because such a low percentage of patients even have a match with the gene, a negative result doesn’t provide helpful information, Dr. Ming said. Patients with a match should limit their sun exposure and see a
dermatologist routinely. Eventually there could be an intervention, but not now. “I don’t recommend getting tested because the results won’t change what I do,” he said. If a patient wants to be tested, Dr. Ming sends him/her to a geneticist and a genetic counselor.

The third dilemma is what dermatologists should know about second primary melanomas. Their prevalence varies greatly, according to population studies. Most estimates put the risk of developing them in the three percent to five percent range, he said. Between 10% and 30% of patients with two melanomas will develop another. Studies suggest that patients at increased risk for a second primary tumor include those with a family history, clinically dysplastic nevi, and the CDKN2A mutation. Some studies say patients with lentigo maligna, relatively fewer sunburns, and increased number of nevi are at higher risk. Most second melanomas are thinner than the first one, Dr. Ming noted, probably due to increased surveillance of these patients.

Anecdotally speaking, the second melanoma tends to occur in a similar location to the first one.

The fourth dilemma is how to use the recent changes to the American Joint Committee on Cancer Melanoma Staging System and its staging manual now in its seventh edition. Dr. Ming reviewed the changes, such as the clarification of the staging definition of metastatic melanoma from an unknown primary site; isolated metastases arising in lymph nodes, skin, and subcutaneous tissues are to be categorized as Stage III rather than Stage IV. Another significant change is that mitotic rate is now used as an independent risk factor of T1b melanomas, replacing Clark’s level. Many studies identify mitotic rate as being more closely associated with outcomes than Clark’s level, he noted. If the tumor lacks ulceration or mitosis, it will be staged as T1a. The committee recommends that Breslow thickness, histologic ulceration, dermal mitotic rate per mm, and microsatellitosis (if present) should be reported. This information is necessary for accurately staging melanoma.

The fifth dilemma addresses new treatments for unresectable metastatic melanoma. Prior to 2011, there were not many options to offer patients with Stage IV disease, Dr. Ming said. Their overall prognosis was poor with survival estimated at six to nine months; five-year survival was less than five percent. In 2011, vemurafenib and Ipilimumab were approved. In one study, patients taking vemurafenib had a 75% partial response and 12% had a complete response. In a second larger study, 48% of patients had a complete or partial response. But patients can develop resistance to the drug. Because of toxic side effects, 40% of patients needed a dose reduction. In two studies, patients taking ipilimumab almost doubled their median survival rate to 10 and 11 months, respectively. “We still have a long way to go as we do not have a cure for melanoma,” he concluded.
fusidic acid, have been reported and are on the rise, Dr. Ghali said.

After providing a history of bleach and reviewing its mechanism of action, he noted that a bath of sodium hypochlorite (equivalent to approximately one-half cup of bleach in 13 gallons of water, or one quarter-filled bathtub) was most effective at killing multiple community-acquired MRSA strains after five minutes. Dr. Ghali reviewed various bleach dilutions and commercially available products with similar properties.

Next, he reviewed the connection between Staphylococcus aureus and AD. Skin with AD is deficient in antimicrobial peptides. Additionally, superantigens of S. aureus cause T-cell dysfunction and S. aureus colonization is much higher in atopic patients. In severe cases of AD, S. aureus is more common. In his opinion, there is a continuum between colonization and infection. Distinguishing between the two is difficult. Patients can go from one to the other; seeing the patient over time is the best way to make that determination. “What you may see as colonized one day may look infected the next day,” Dr. Ghali said.

Approximately 35% of his AD patients who are infected grow out MRSA. In a recent study, chronic use of dilute bleach baths with intermittent intranasal application of mupirocin ointment decreased the clinical severity of AD in patients with clinical signs of secondary bacterial infections. This study shows that bleach baths are a beneficial adjunctive therapy. Although the study noted that patients with AD do not seem to have increased susceptibility to infection or colonization with resistant strains of S. aureus, he disagrees. A recent Cochrane Review, however, failed to find any evidence that commonly used anti-staphylococcal interventions are clinically helpful in people with eczema who are not clinically infected. Sometimes colonization versus infection is a slippery slope, he noted. Reserve cultures for those who are refractory and not responding to treatment, Dr. Ghali added.

In a 12-week pilot study he conducted, a body wash formulated with sodium hypochlorite used in conjunction with standard treatment regimen in 18 teenage patients had a 98% kill rate at two minutes and a 99.9 at three and five minutes for S. aureus. Dr. Ghali concluded that the body wash was an effective adjunctive therapy in AD, similar to traditional bleach baths, the latter of which typically has poor compliance, especially with older teens.

For primary staph SSTIs, he recommends containment maintenance strategies including the use of antimicrobial soaps, topical antibiotics, chlorhexidine, and sodium hypochlorite. For secondary SSTIs, Dr. Ghali recommends the use of topical antibiotics and sodium hypochlorite.

Moving on to refractory warts, he said that you can get better control of them using liquid nitrogen versus an application of verruca-freeze or histofreeze. Dr. Ghali also uses cantharadin, which is not FDA approved, but is included under the Bulk Substance Act for compounding to physicians. It can be compounded or ordered from Canada. The main advantage is that it is a painless procedure. If used on the dorsal hand, ring warts commonly result. He uses it only for warts on the palms and/or soles. He does not use it on the fingers, cuticles, base, or other areas. Additionally, there is a high risk of ring warts with “over-freezing” using over the counter (OTC) products or histofreeze/verrula-freeze.

Dr. Ghali favors using immunotherapy, which works as follows: an in-office application of squaric acid to a skin site (usually the arm) induces contact allergy (sensitization) and at home patients use a lower concentration painted on warts to induce immune response. Squaric acid is more popular with pediatric patients. If there is no response in two months, he doubles the strength. Beware of the “recall” phenomena at the original sensitization site when the patient begins applying a weaker percentage of squaric acid. While its presence correlates well with a good response, its absence does not mean a failure as the majority of responders do not have this reaction. Dr. Ghali avoids using it on the face, neck and groin. Squaric acid is approximately 70% effective and seems to work best against plantar warts. Treatment duration is two to four months. Among its advantages, squaric acid is not painful, may be combined with other treatments, and offers ease of sensitization in most patients. If the patient develops contact dermatitis, decrease treatment applications and use a potent topical steroid or oral steroid if the side effect is severe. If the treatment fails, using a higher percentage for the outpatient protocol may be an option.

Regarding vitiligo, treatment using topical options is location-dependent, he noted. Several case series in the literature discuss the off-label use of tacrolimus. “Location and patience are the take home message,” Dr. Ghali said. Tacrolimus is slow to work, taking four to six months. Better results are seen when it is combined with “cautious” natural ultraviolet (UV) exposure. It works better on thin skin and darker skin tones and is best for treatment on the face and neck. Children respond better than adults; the shorter the disease duration, the better the response. Combination therapy of tacrolimus plus narrowband UVB therapy is vastly more effective than either therapy alone, according to studies. Its use requires signed consent following a discussion of possible skin cancer risk.

Even more off-label is the use of topical oxsoralen in a diluted ointment. Dr. Ghali advises to be cautious with this therapy as he has heard of lawsuits, so choosing the right patient is imperative. So is choosing the right body site as it is better for treatment on the trunc and extremities. It should be avoided for treatment on the face as a reaction (of blisters) is too unpredictable. Topical steroids can work well in some areas especially the knees and shins. It tends not to work as well near the ankles, hands, or groin. He uses fairly strong steroids intermittently.

Among the breakthroughs Dr. Ghali reviewed were propranolol for HOIs and sirolimus for angiofibromas. Many studies have shown that topical timolol maleate offers a quick direct inhibitory effect on the growth of HOIs, followed by slower regression. It is best for superficial types. For angiofibromas, there are initial reports that topical sirolimus improves both the hypopigmented macules and “red plaque” associated with tuberous sclerosis, a hallmark skin finding of angiofibromas. He is currently trying it on forehead fibrous plaques.
Cosmeceuticals

Dermatologists need to know about cosmeceuticals because patients are increasingly asking “our expert opinion” about them, noted Steve Grekin, D.O.

The term “cosmeceutical” was coined in 1984 to describe a unique category of products somewhere on the continuum between drugs and cosmetics. These products are expected to have both cosmetic and therapeutic or physiologic benefits.

Although the Federal Food, Drug, and Cosmetic Act defines both cosmetics and drugs, it does not recognize the category “cosmeceutical.” A cosmeceutical can be a drug, cosmetic, or combination thereof. Creative marketing can promote the benefits of cosmeceuticals without outright claims regarding their physiologic or therapeutic benefits. Thus, they are advertised as offering, for example, more even skin tone, improved skin texture, increased skin radiance, and decreased appearance of skin wrinkling, as well as enhanced anti-aging benefits. Although the FDA does not regulate cosmeceuticals, the agency has provided guidelines for cosmetic good manufacturing practice to ensure against adulterated or mislabeled products. The FDA may conduct research on cosmetic products and ingredients to address safety concerns. Additionally, cosmeceuticals are regulated by the Federal Trade Commission, which is charged with investigating advertising claims of pharmaceutical properties to assess the soundness of the advertisement.

Product efficacy is usually tested using the final formulation, making it challenging to separate out the effect of an individual ingredient, Dr. Grekin said. Most cosmeceuticals are made from ingredients that already have a proven safety record in the cosmetic market. New, raw ingredients generally undergo extensive animal testing to determine if the ingredient is appropriate for human use. No well-established, large cosmetic/cosmeceutical corporation wants to tarnish its reputation by putting out products that would be deemed unsafe or untested in some fashion, he noted. The “catch 22” is that invasive evaluations of the effect of the product on the skin cannot be performed, he said, because this would indicate that, in fact, the product has pharmacological effects rather than cosmetic benefits.

Various, non-invasive, methods are used to test the efficacy of cosmeceuticals, Dr. Grekin stated. For example, skin moisturization is measured by evaporimetry or corneometry, improvement in fine lines and wrinkles is measured by profilometry, improvement in skin color/tone is measured by Doppler flowmetry or chromametry, improvement in skin thickness is measured by A-scan ultrasound imaging, and finally improvement in any of the above characteristics is measured by the human eye, ideally in well-controlled, double-blind studies. Good quality, well-controlled studies compare the efficacy of the vehicle versus the vehicle plus active ingredient, in order to determine the effect of the individual active ingredient. Vehicles can boost the efficacy of an active ingredient or inactivate it, he added.

Next, Dr. Grekin examined the evidence regarding the efficacy of common ingredients, specifically antioxidants, growth factors, peptides, anti-inflammatories/botanicals, polysaccharides, and pigment lightening agents. As an example, hydroquinone, which is known for its suppressive effects on melanin synthesis, has been used for years in topical concentrations of two percent to four percent, either alone or in combination with tretinoin, to successfully improve melasma. But in 2006, the FDA announced that it may no longer be safe as it may have carcinogenic properties. Hydroquinone has been banned in OTC preparations in Europe, Australia, and Japan, but is still available in such preparations in the United States. He also discussed azelaic acid, niacinamide, and vitamins E and C, noting that many of these ingredients demonstrated benefits when used in higher concentrations than are available in OTC products.

Regarding retinoid, topical cosmeceuticals containing retinol and retinal theoretically work because once absorbed they are metabolized to retinoic acid, which induces pharmacological activity, Dr. Grekin explained. Unfortunately, only a small amount of retinol and retinal can be converted by the skin, accounting for the increased efficacy seen with prescription preparations containing retinoic acid. Retinoids is one of the most studied ingredients in cosmeceuticals as it is an effective topical treatment for photoaging, acne, and numerous dermatological disorders. Tretinoin is considered to be one of the most potent compounds available for treating the signs of aging and/or photodamaged skin. However, side effects, such as burning and scaling, can limit its use and acceptance. Retinol is available OTC and is considered the “gold standard” cosmeceutical in anti-aging, he said, as it is less irritating to the skin and tolerated better than prescription tretinoin.

Alpha hydroxy acids are commonly used in cosmeceuticals due to their hydrophilic properties, Dr. Grekin noted. Many forms and various sources exist, although lactic acid and glycolic acid are the most widely studied forms of AHAs because their molecular size allows effective penetration into the top layers of skin.

Citing other common ingredients, Dr. Grekin said that soy-derived products are believed to have a range of dermatologic benefits, from depigmentation to prevention of photodamage and photoaging. Kinetin, a plant growth factor, has been shown to delay aging in fibroblasts, resulting in improved skin texture, color, blotchiness, fine wrinkles, and skin barrier function. Naturally occurring antioxidants are used in various cosmeceutical products. Specifically, green tea polyphenols have both antioxidant and anti-inflammatory properties, and has been suggested to have an anti-carcinogenic effect from UV radiation. However, no clinical trials have ever shown long-term benefits of green tea, he added. Topical peptides are supposed to enhance collagen production, relax dynamic skin wrinkling, and improve skin hydration and barrier function. They may be a better option for patients who do not tolerate retinoids well, Dr. Grekin said. One topical peptide, argireline, has been shown to inhibit neurotransmitter release with potency similar to that of Botulinum toxin A, but with much lower efficacy. At some point, it may prove to be a milder alternative for patients who fear needles. The cost of peptides poses a challenge to cosmeceutical companies,
he added, especially if they have low potency and require greater concentrations to achieve efficacy.

New in cosmeceuticals is resveratrol, a polyphenolic antioxidant with diverse biological effects found in high concentrations in grapes and red wine, which may prove valuable in preserving dermal collagen. Although objective clinical studies confirming these benefits are lacking, Dr. Grekin noted, the science behind resveratrol is plentiful and promising. An extract from the java tea plant has been shown to decrease sebum production to control oily skin. A study using a “cellulite cocktail” of retinoids, algae extracts, conjugated linoleic acid, and glaucine suggests that combinations of cosmeceuticals can act as a powerful mixture to stimulate fat breakdown.

When evaluating a cosmeceutical product, logically assess whether the product is able to penetrate the stratum corneum to the level of the desired target and can do what it claims to do, he advised. Also, determine whether there are peer-reviewed, double-blinded, placebo-controlled, statistically significant clinical trials regarding the efficacy of the product. “You have to read the research with an ounce of skepticism because you don’t want patients spending a lot of money,” Dr. Grekin said. “You want them to do procedures you know will get results.”

Unfortunately, many of the studies regarding these products are small. More importantly, the claims regarding what they can do in-vivo is limited by these products being labeled as cosmeceuticals. “When talking with patients, you need to figure out what matters to them,” he concluded. “It’s important to educate the patient and yourself by staying up to date with this rapidly expanding and evolving field of cosmetic medicine.”
Great Cases

Cindy Hoffman, D.O., Program Director at NYCOM/St. Barnabas Hospital, kicked off Tuesday’s lectures with Great Cases from Osteopathic Teaching Programs.

Richard Miller, D.O., Program Director at NSUCOM/Largo Medical Center, presented a case of microcystic adenexal carcinoma, which he first diagnosed as trichoadenoma. After attempting to excise this rare solitary tumor to prevent recurrence, he found perineural invasion. Microcystic adenexal carcinoma commonly masquerades as BCCs. Standard of care is Mohs micrographic surgery, but excision should be considered when the pathology is reassuring; they can worsen from radiation. Microcystic adenexal carcinoma should always be considered in the differential diagnosis of slow growing tumors in the head and neck, Dr. Miller noted.

David Horowitz, D.O., Program Director at Western University Pacific Hospital, presented a case of Gottron’s syndrome, which is due to spontaneous mutation of the loricrin gene. There is a family history in only half of patients. Although it can be managed using topical and oral retinoids, this case involved a five-year-old boy who should not be prescribed oral retinoids. The patient who was treated with topical retinoids had an approximately 30% improvement.

Bradley Glick, D.O., Program Director at Wellington Regional Medical Center, presented a case that started out with the diagnosis of pyoderma gangrenosum (PG), but eventually became Wegener’s granulomatosis (WG). He treated the 50-year-old male patient with mini-pulse steroids, intravenous (IV) vancomycin, IV fluid support, wound care, and painkillers. Further testing showed the patient to be positive for c-ANCA, a relatively sensitive and highly specific marker for WG. Treatment of this rare disease, which can be problematic to diagnose because of its varied clinical manifestations, requires aggressive management of high-dose steroids and immunosuppressive therapy. The patient is slowly improving.

Stephen Kessler, D.O., Program Director at Alta Dermatology, presented a case of erucism caused by a sting from a caterpillar moth. Within minutes of touching “something in the bushes,” the patient had a stinging sensation and within one hour the eruption appeared. The 44-year-old male presented with a five-day history of a rash on his right hand. A dermoscopic exam, which revealed spiral projections coming out of the skin, helped Dr. Kessler diagnose the case.

Vernon Mackey, D.O., Program Director at Advanced Desert Dermatology, reviewed a case of psoriasis that was resolved when the patient underwent a tonsillectomy. A 23-year-old female patient with a four-year history of psoriasis had previously been treated with topical steroids, UVB, liquid coal tar, and adalimumab, some of which worked. She declined additional treatments as she wanted to start a family. After the patient had a tonsillectomy, she had a complete resolution of psoriasis. Dr. Mackey pointed out that a strong association between strep throat infections and acute guttate psoriasis is well known. Whether there is an indication for tonsillectomy of patients with chronic psoriasis remains to be defined.

Suzanne Sirota Rozenberg, D.O., Assistant Program Director at St. John’s Episcopal Hospital, discussed how to navigate the interdisciplinary approach when diagnosing patients. In her example, a diagnostic delay of malignant melanoma occurred. After having “a dark spot” for more than 20 years, the patient came to see a physician. A previous biopsy report suggesting it was a benign lentigo, an unsigned pathology report, a small sample, and scheduling problems for an additional biopsy contributed to a several-month delay. She concluded that communication is essential when using a multidisciplinary approach. Dr. Sirota Rozenberg cautioned against incriminating other healthcare providers and assigning blame.

Lloyd Cleaver, D.O., Program Director at Northeast Regional Medical Center, discussed side effects of vemurafenib for the treatment of melanoma using the case of a 79-year-old female patient treated for unresectable melanoma as an example. Among the common side effects she experienced were acneiform eruption, papular eruption, satellite tumors, alopecia, photosensitivity, and rash. The most common side effect, cutaneous SCC, occurs in approximately 24% of patients, he noted. They grow rapidly and almost all are the KA type, Dr. Cleaver said. After the patient was treated with vemurafenib, KA excision, and Mohs surgery, her follow-up has been negative.
The word “tattoo” is derived from the Polynesian word “tatau” meaning to tap and the Tahitian word “tatu” meaning to mark, explained Melinda Greenfield, D.O., as she explored the curious history of body art, piercing, and personal grooming during her presentation.

The earliest known tattoos were found on Otzi the iceman who was carbon-dated to be 5,200-years-old. He had 59 tattoos that corresponded to acupuncture points and areas of osteoarthritis. The tattooed dots and small crosses on his lower spine, right knee, and ankle were thought to be of therapeutic value.

In Egypt, tattoos dating back 4,000 years were discovered. Originally, they appeared to be an exclusive female practice. They were thought to be on women of “dubious” status, she said, but then they were found on in the tomb of Amunet, a high-status priestess. Some believe that these patterns of dots or dashes on the abdomen, thighs, and arms were the mark of prostitutes or meant to protect against sexually transmitted diseases. Others believe these were placed to protect women during childbirth. During pregnancy, these net-like dots would expand in a protective fashion. The earliest tattoo found that was not an abstract design was of Bes who was the protector of households, mothers, and children. Women would tattoo her image on their thighs during pregnancy.

The Japanese word for tattooing is “irezumi” meaning to insert ink. Tattooing has been practiced in Japan for 10,000 years. From 300-1870, Japan marked its criminals with tattoos. Criminals then started covering up their shameful marks with more decorative tattoos. In 1870, the Japanese government banned tattoos, driving the practice underground. It was again legalized in 1945 at the end of the Second World War. However, tattooing never completely lost its association with the criminal underworld and people displaying tattoos are still banned in certain public places such as health clubs and swimming pools.

Chinese tattoos have many similarities to Japanese tattoos from their historical origins to their use to mark criminals, Dr. Greenfield noted. The most popular are the Chinese character symbols known as “hanzi,” which are far more popular in Western Culture than in China itself. Ironically, many of the hanzi used in American tattoos are inaccurate and complete gibberish, she said.

Other ancient cultures used tattoos, as well. Native Americans used extensive facial and body tattoos. The Polynesians used highly elaborate geometric designs that sometimes covered the entire body. The Maori culture of New Zealand tattooed their faces.

With the rise of Christianity in Europe, tattooing faded out. Sailors, however, continued to circle the globe and return home with the art of the various tribes and regions they encountered. Some sailors got a tattoo with every voyage. A lighthouse was meant to guide a sailor home, a turtle indicated that he crossed the equator, a dragon meant the sailor crossed the international dateline, and an anchor meant he sailed the Atlantic Ocean.

To determine who gets tattoos today, the Journal of the American Academy of Dermatology (JAAD) recently conducted a random telephone survey calling 500 individuals, ages 18 to 50. Twenty-four percent of respondents had tattoos and 14% had piercings. Tattooing was equally common in both sexes; body piercing was more common in women. The arm was the most common location of a tattoo on men and the ankle on women. Common associations with tattoos were lack of religious affiliation and extended jail time as well as previous drinking and drug use. Complications with piercings included broken teeth and increases in jewelry allergies. A 2012 Harris survey interviewed 2016 adults and found that 21% of respondents had at least one tattoo. While only 11% of 50- to 64-year-olds are inked, a whopping 38% of those in their 30s report tattoos. Eighty-six percent of survey respondents said they have never regretted their decision, with 30% saying it makes them feel sexy. Among the un-tattooed, 45% said that a person with a tattoo is actually less sexy.

No federal regulations exist for tattoo parlors and states that are regulated forbid tattoos or piercings on a minor, she stated. However, in Colorado, Florida, Idaho, and Louisiana minors can be tattooed with signed parental permission.

Basically, state regulations restrict an artist from tattooing any person who is jaundiced or any part of the skin that has a rash, boils, infection, or appears inflamed. The artist must wear gloves, wash their hands and arms, and use a different needle for each patron. Infections must be reported to the local health department within 48 hours. Additionally, patrons must be sober and in good general health. There must be a separate area for tattooing with a clean bathroom, and the equipment must be sterilized in an autoclave. Regulated states require tattoo parlors to obtain permits and a health department inspection before opening. To check regulations in your state, Dr. Greenfield suggested visiting the website www.aataattoodirectory.com.

Moving to piercing, she said that nose piercing was first recorded in the Middle East, approximately 4,000 years ago. In the bible in Genesis, Rebekah received a “golden earring,” which translates as “nose ring,” as a dowry gift for marrying Isaac. This tradition is still followed in nomadic tribes in Africa today, Dr. Greenfield said. The size of the ring denotes the wealth of the family, and is “security” for the wife in case of divorce.
Nose piercing was brought to India in the 16th century. In India, a stud is worn in the left nostril, sometimes joined by a chain to the ear. In Ayurvedic medicine, the nose is associated with the female reproductive organs. Piercing is supposed to make childbirth easier and lessen menstrual pain.

In the west, nose piercing first appeared among hippies who traveled to India in the late 1960s. It was later adopted by the punk movement as a sign of rebellion in the 1970s.

Ear lobe piercing was found on mummified bodies dating back more than 5,000 years, with holes as large as 11 mm, she said. Ears were pierced for magical purposes. Primitive tribes believed that demons entered the body through the ear. Because they are repelled by metal, ear piercing prevents them from entering the body. Sailors pierced their ears so that if their body washed up somewhere the earrings could pay for a Christian burial.

Lip piercing is widely practiced throughout the world, as well. Among the Dogon Tribe of Mali, lip piercing was done for religious purposes. Lips are either pierced with a ring or a labret, which consists of a pin of wood, ivory, metal, or even crystals.

A “Prince Albert” is probably the most common genital piercing. Named after Queen Victoria’s husband, Albert had his penis pierced with a “dressing ring” so he could manipulate his privates to prevent an unseemly bulge when he wore tight trousers.

Regarding “landscapes,” a 2009 poll stated that 50% of women between the ages of 18 and 25 admit to shaving their pubic hair, and 25% of men either shave or trim it. In a study commissioned by Wilkinson, 62% of women want men to shave their pubic hair, and the men in the study supposedly stated that “unshaved women have fewer sex prospects,” she said.

From medieval and classical European art to the twentieth century, paintings and sculpture in the Western tradition usually depicted women and men without pubic hair. Francisco Goya’s *The Nude Maja* (circa 1800) is considered the first European painting to show a woman’s pubic hair; the painting was considered quite pornographic at the time.

Trimming or removing pubic hair is customary in many cultures, Dr. Greenfield said. In Islamic societies, removing pubic hair is a religiously endorsed practice. In contrast, the Sikh religion forbids cutting or shaving any bodily hair. In Japan, laser depilation appears to be widespread. Europeans have been generally accepting of body hair.

When the bikini became popular in the 1970s, women faced increased pressure to remove pubic hair in order to wear the latest fashion. With the increased popularity of “shaved styles,” more adults and teens are jumping on the bandwagon, she said. “Along with this trend come issues such as folliculitis, infected cysts, contact dermatitis, and other issues we couldn’t even begin to imagine,” Dr. Greenfield concluded. “As physicians, we need to be prepared to address the issues and be open to these new trends.”

Stephen M. Purcell, D.O., presented several clinical and clinical-histopathological cases, offering a pearl of wisdom with each.

Among those he presented was the case of a 10-year-old previously healthy Hispanic female. Two days after developing a 104° fever accompanied by myalgias, abdominal pain, headache, minor epistaxis, and oral ulcers, she became confused and/or unconscious and developed tonic-clonic seizures. The patient had been swimming in a lake one week prior to becoming ill. She had no abnormal skin findings and her cultures were negative. His impression was that the patient had encephalopathy and refractory seizures of unknown etiology.

Dr. Purcell performed a dermatology consult to rule out rabies. He had to contact the state health department prior to submitting samples to the rabies laboratory at the Centers for Disease Control and Prevention. One of the samples that Dr. Purcell submitted was a nuchal biopsy, which he believes dermatologists are best equipped to perform. A nuchal biopsy requires a 5 to 6 mm punch from the posterior neck at the hairline. It should include a minimum of 10 hair follicles and be of sufficient depth to include cutaneous nerves at the base of the follicle, he said. It is greater than 98% sensitive. The patient who was diagnosed with rabies improved on systemic corticosteroids. The pearl: nuchal biopsy may be helpful in the diagnosis of rabies.

Another case involved a 47-year-old male who was diagnosed with basal cell nevus syndrome (BCNS) at age 18 based on the findings of odontogenic keratocysts, calcification of the falx cerebri, and palmar pits. When the patient was 33, he began to develop multiple BCCs requiring numerous surgeries. In May of 2010, the patient enrolled in a trial of GDC-0449, an oral drug that inhibits Hedgehog pathway signaling, that ended in November of 2011. He experienced significant side effects including recalcitrant nausea and loss of taste resulting in a 25-pound weight loss. Additionally, the patient experienced abdominal pain, diarrhea, fatigue, and generalized alopecia. His symptoms...
resolved after discontinuation of the trial, suggesting he was not in the placebo arm. The patient’s existing BCCs resolved and he has not developed any new tumors since. Interestingly, his palmar pits disappeared. In a multicenter clinical study of 96 patients with locally advanced or metastatic BCC treated with vismodegib, 30% of those with metastatic disease had a partial response while 21% of those with local advanced disease had a complete response and 22% had a partial response. Of the 96 patients evaluated, 21% carried a diagnosis of BCNS. In a Phase II clinical trial, vismodegib was evaluated in patients with BCNS. The incidence of new BCCs after eight months in the vismodegib arm was 0.07 cancers per month and in the control arm it was 1.74 cancers per month. Not only was there a 25-fold reduction in the rate of new BCCs, but patients’ existing tumors decreased in size within the first month, and their palmoplantar pits and odontogenic keratocysts cleared. No tumor resistance was observed. Common side effects included loss of taste, muscle spasms, and alopecia. All side effects reversed one month after discontinuation of the drug. After stopping therapy, tumors did not return to baseline size or increase in number during the next six months. The pearl: vismodogib may be beneficial in patients with BCNS or those with unresectable BCC.

Another case involved a 45-year-old female with more than a six-year history of intermittent recurrent pruritic dermatitis. She had a medical history of hypothyroidism and granuloma annulare. The patient had a family history of allergies, diabetes, and heart disease, but no known drug allergy. She worked as an assembler/upholsterer in a furniture factory. Physical examination revealed patchy eruption of small erythematous papules especially on the upper extremities, hips, and thighs. Histopathology showed spongiodermititis. The patient had a positive reaction to fragrance, thimerosal, methylidibromoglutaronitrile, carba mix, methylchloroisothiazolinone, and dithiodimorpholine. Despite avoidance of known allergens, the dermatitis continued to recur. The onset of eruption could not be related to environmental exposures. It was controlled with oral antihistamines and topical corticosteroids. Ultimately, the patient determined that her dermatitis flared approximately 10 to 14 days prior to her menses. Thus, she was diagnosed with autoimmune progesterone dermatosis, a rare hypersensitivity reaction to endogenous progesterone. It is characteristic of cyclical cutaneous eruptions that flare during the luteal phase of the menstrual cycle when progesterone levels peak, and resolves partially or completely a few days after menses. Cutaneous manifestations include urticaria, eczematous eruptions, vesiculopustular eruptions, fixed drug type eruptions, stomatitis, erythema multiforme, and anaphylaxis. Treatment options include topical corticosteroids, oral antihistamines, and systemic corticosteroids; ovulation inhibition with pharmaceutical agents and; oophorectomy for refractory cases. Other therapies, such as thalidomide, also have been used with success. The pearl: recalcitrant, cyclical dermatitis may be autoimmune progesterone dermatitis.

A 64-year-old male presented with a six-month history of hand dermatitis that came on slowly with blistering, weeping, and cracking. It was unresponsive to topical corticosteroids as well as topical and oral antibiotics. He had a medical history of melanoma, atrial fibrillation, and cerebrovascular accident. A physical exam revealed pink, scaling, and crusted plaques with fissures on the palms and fingers. The differential diagnosis included contact dermatitis, endogenous dermatitis, psoriasis, and mycosis fungoides (MF). Dr. Purcell diagnosed the patient with Woringer-Kollop disease, also known as pagetoid reticulosis or MF palmaris et plantaris. The patient was treated with topical PUVA and had a good response. The pearl: resistant hand dermatitis may be MF.

**PDT for Skin Cancers, AKs**

The use of photodynamic therapy (PDT) to treat skin cancer raises concerns because of high recurrence rates, and while PDT may have a cosmetic role in treating actinic keratoses (AKs), there is no evidence that its use prevents skin cancer, noted Anthony Dixon, M.B., B.S., Ph.D., Director of Postgraduate Education, Australasian College of Cutaneous Oncology.

Reviewing possible indications for PDT in the treatment of skin cancer, he said that its use for treating invasive SCC was unacceptable as studies have shown poor outcomes. But its use for treating Bowen’s disease is an approximately 90% clearance rate; comparable with cryotherapy. Another recent trial showed a 76% response rate in six to eight months; lower than Dr. Dixon would have expected. A dozen studies demonstrated clearance rates of approximately 90%, but recurrence rates between 18% and 38% when PDT was used to treat superficial BCC. When used to treat nodular BCC, aminolevulonic acid (ALA) PDT demonstrated a 30% failure rate in patients followed for three years compared with
a 2.3% failure rate for surgery. Studies also have shown PDT to have high recurrence rates, such as one-third of BCCs recurring after two years, which Dr. Dixon says is unacceptable. A recent study showed that when BCCs recur, they are often more aggressive, he said. It's unclear whether the PDT causes the BCCs to be more aggressive or whether they would have been anyway. But other recent studies have shown recurrence rates similar for both superficial and nodular BCCs. Despite the high failure and recurrence rates, PDT does show a "good" to "excellent" cosmesis rate in the 90th percentile in studies. In summary, Dr. Dixon said PDT is neither good for treating SCCs nor nodular BCCs. However, it could be considered an option for treating superficial BCCs and AKs.

When approached by a company, which was marketing a new ALA PDT product, to conduct a randomized, clinical trial evaluating the efficacy of ALA PDT to treat face field AKs, Dr. Dixon was hoping the study would determine whether such treatment would reduce the risk of future skin cancers developing. Consequently, Dr. Dixon agreed to participate as lead researcher in the study. The inclusion criterion was previous invasive skin cancer on the face. The study was being conducted in six centres across Australia. Patients in the intervention group received two treatments of ALA PDT two weeks apart and followed up for two years. Suspicious lesions were biopsied and cancers excised.

Dr. Dixon became immediately concerned when early in the study the company changed the protocol to include an analgesic agent that could not be substantiated. Moreover, 17%—or six of 35 patients—had severe adverse events. Many patients described experiencing "the worse pain ever" while others had ulceration, blistering, and cracking of the skin. Some patients had full thickness burns while others had permanent fibrosing scars.

Although the Ethics Committee stopped the trial, Dr. Dixon continued to monitor the patients. Over the next three years, 38% of patients developed new skin cancers on the face; there was no difference between the intervention and control group. All new cancers were BCCs or SCCs, except for two patients in the intervention group who had lentigo maligna and Merkel cell cancer. Post-treatment pain was prolonged and more severe, and worse than that associated with complex face surgery. In the end, three patients had permanent scarring, seven had severe pain, and none had a reduction in new skin cancers.

When Dr. Dixon submitted the data to the Therapeutic Goods Administration (TGA), Australia's equivalent of the FDA, the TGA responded saying that the agency had no knowledge of such a study being conducted.
This company, which claims its product is a “natural cosmetic” and therefore does not need TGA approval, continues to market the product through “independent experts.” Dr. Dixon acknowledges that had he not taken the company’s word, done his due diligence, and had not been clouded by the belief that he was helping out, he would not have participated in the trial in the first place. From now on, Dr. Dixon vows to use only tested and approved PDT products.

“I know that US doctors complain about the FDA and how it is too slow in approving treatments, but compared with the TGA, the FDA is terrific and much tougher,” he said. “Australia really needs to toughen up and the TGA needs to have the power to act in order to protect Australians.”

Dr. Dixon concluded his presentation by raising the question of whether treatment of BCCs with PDT results in such high recurrence rates because the therapy sharply reduces the number of Langerhans cells. Studies have shown that when ALA PDT is put on normal skin, it reduces Langerhans cells with a sustained effect of 24 hours. This may suggest that PDT has an effecting anti-tumor response.

Classification, Treatment of Hand Eczema

Knowing the period prevalence, which is the number of patients with outbreaks during a period of time, will reveal the true burden of disease because hand eczema waxes and wanes, according to Peter Saitta, D.O. The period prevalence of hand eczema is estimated to be between 2% and 10%.

Risk factors for hand eczema include AD, allergic rhinitis/asthma, certain occupations, and wet irritant exposure. Women tend to have occupations that increase their risk. Among those are hairdressers, nurses, bakers, office workers, and factory workers. Women also tend to have more exposure to liquids than men in their personal lives. Risk factors that contribute to a poor prognosis include having allergic contact dermatitis, a delayed onset of effective treatment, AD, a greater area of involved skin, and more than one-year duration.

The most common cause of irritant contact dermatitis is “wet work” involving water, mechanic/machinery oils, or detergents. Other causes are tight-fitting gloves and friction. Studies define wet work as requiring more than 20 handwashes daily or having wet hands or wearing gloves more than two cumulative hours daily. Widespread dermatitis that starts on the hands is more likely caused by allergic contact dermatitis, he added. Allergic contact dermatitis is much more common in occupational exposures compared with private exposures. That’s why it is helpful to ask the patient what he/she does, Dr. Saitta said. Other than AD, genetic factors are unknown.

Regarding a morphology classification, the guidelines of the Danish Contact Dermatitis Group suggest that hand dermatitis consists of chronic dry fissured hand eczema, vesicular hand eczema, hyperkeratotic hand eczema, interdigital hand eczema, pulpitis, and nummular hand eczema. Dr. Saitta proposes that a mixed pattern demonstrating multiple morphologies should be added because that is how hand dermatitis presents in half the cases. Additionally, the morphology changes frequently. The problem with the current classification is that it is good for academic pursuit, he said, but not practical on a day-to-day basis. Because there is no clear link between morphology and etiology, some question the need of a classification system based on these, he stated.

With chronic dry fissured hand eczema, the entire hand onto the wrist is prune-like and very dry, which results in fissuring, Dr. Saitta said. The differential diagnosis includes palmoplantar psoriasis, which is well-marginated, cuts off abruptly at the wrist, and has micaceous scales. In contrast vesicular hand eczema is intermittent; intensely pruritic; occurs on the palms/soles, nail, and sides of fingers; attacks between 1 and 10 months; and has two historical terms: pompholyx and dyshidrosis.

Experts disagree about the presence of erythema in the dyshidrosiform pattern, which has a progression of lesions. In the early stage, these lesions are vesicular, but in the late stage, there is a chronic dry fissured presentation studded with pinpoint necrotic vesicles. Dr. Saitta describes it as more of a “wet glazed look with pinpoint necrotic vesicles.” The pompholyx pattern, which is very rare, is a single episode of a vesicular and bullous eruption of the palms and soles. “It is a dramatically different presentation,” he said. Next, Dr. Saitta showed pictures of, and described, palmoplantar pustulosis, hyperkeratotic hand eczema, tinea manuum, interdigital hand eczema, erosio interdigitale blastomycetica, scabies, pulpitis, and nummular dermatitis.

To simplify making a diagnosis, Dr. Saitta suggests considering hand eczema an eczematous process. Acute cases present with vesicles/bullae whereas subacute and/or chronic cases present as scaling and erythema. If it’s acute, check the feet because foot involvement in hand eczema is rare. To evaluate if the cause is an irritant, ask the patient if he/she frequently touches liquids, including water, on a daily basis. To evaluate if it’s AD, ask if the patient had childhood eczema, allergies, or asthma. If it’s allergic dermatitis, ask what the patient does for a living. An additional work-up involves patch
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testing. Only 21% of patch tests are positive; nearly 100% of cases are due to nickel and 30% are relevant.

Regarding treatment, faster clearance at the disease onset lowers the risk of chronicity, he said. Typically, hand eczema occurs once or randomly so there’s no reason not to use systemic or topical steroids to treat it. Don’t stop treatment immediately after it improves; that’s the most common mistake physicians make, he said. Classically, hand eczema flares when the treatment is stopped. Be sure to shake the patient’s hand as it is not contagious. Understand that a therapy that worked before, might not work again. Hand eczema does get better with time; the period prevalence decreases with aging. Giving the patient a positive outlook is important.

Among the tips that Dr. Saitta gives his patients are decrease the number of handwashes daily, apply an emollient often, and use gloves when doing wet or dirty work. Alcohol-based disinfectants are less irritating to the skin than soap and water. The emollient should be applied within two to three minutes of washing and as often as they wish. The greasier the emollient is the better. It should be free of fragrance. The gloves can be latex or vinyl, tight-fitting, cotton-lined, and changed when damp.

Cutaneous Lymphomas

Whether they are indolent or aggressive, treatment for primary cutaneous lymphomas requires a multidisciplinary approach, noted Francisca Kartono, D.O. Dermatologists can diagnose cases of cutaneous T-cell lymphoma (CTCL) early on because it commonly presents as contact dermatitis and chronic eczema. A dermatoopathologist can help make the diagnosis, a medical or radiation oncologist may be needed, and the primary care physician (PCP) can help with treatment as he/she knows the patient’s comorbidities, she said. Because patients typically struggle with accepting the diagnosis and then managing the disease, patient support is an essential part of treatment, Dr. Kartono added.

Primary cutaneous lymphomas are a group of diseases with a constellation of morphologic, immunologic, genetic, and clinical criteria. Their behavior is distinct from nodal lymphomas as is their anatomic locations. They are classified as either CTCLs, as in MF and sezyry syndrome (SS), or cutaneous B-cell lymphomas (CBCLs). Secondary cutaneous involvement refers to nodal or systemic lymphoma.

Lymphomas currently represent 4% of all cancers. There are more than 30,000 estimated cases of CTCL in the United States and Canada. The incidence of CTCL is increasing in the United States with approximately 3,000 new cases diagnosed annually.

According to the World Health Organization/European Organization for Research and Treatment of Cancer classification, MF variants of CTCL include folliculotropic, pagetoid reticulosis, and granulomatous slack skin. These MF variants and SS comprise 55% to 65% of all CTCL. Primary CD30+ accounts for 14% of all CTCLs. The significance of the classification is to distinguish clinical behavior and five-year survival rates, Dr. Kartono said. MF is associated with high survival rates.

In most cases, a potent steroid can be used, he said. Next, moderate ones are typically used. Super potent steroids are used much less frequently, but when used, they should be used first. Regarding frequency and length of time, Dr. Saitta said that once daily dosing has equal efficacy as twice daily. He tells patients to apply it at night before bedtime. Treat in two-week intervals. If there is no change, Dr. Saitta recommends switching the steroid. Even switching in the same class can prove to be beneficial.

Tacrolimus, but not pimecrolimus, is an alternative to steroids, he stated. It also can be used in combination with steroids. For example, after initial treatment with steroids, treat with a steroid ointment and tacrolimus for five weeks. Numerous studies show the use of tacrolimus decreases recurrence of hand eczema. He has seen the taper approach work well. The “first blow” may consist of prednisone tapered after the initial dose and/or an intramuscular shot of kenalog. The “second blow” is one of two variations of prednisone dosing. Systemic agents are more effective than topical agents in treating infected hand eczema. Botulinum toxin comes in handy with patients who sweat a lot. Although he doesn’t use UV lights, Dr. Saitta said that UVA is better than UVB and PUVA provides a more even application.

Classic morphology for MF is greater than 3 to 4 cm chronic erythematous patches/plaques, polymorphous, cigarette paper wrinkling, and scaling. In skin of color, there is poikiloderma and reticulated hyperpigmentation. MF mimics chronic eczema, contact dermatitis, and psoriasis. There is a progression from patch to plaque to tumor to erythroderma, she explained. It classically occurs in sun-protected areas and is rare on the face. A diagnostic algorithm was published in the JAAD. (Pimpinelli N, Olsen EA, Santucci M et al. Defining early mycosis fungoides. JAAD 2005:53(6):1053-63.)

For suspected MF, conduct two skin biopsies at different sites. But first discontinue all therapies. Dr. Kartono recommended having a dermatopathologist review the biopsies and also to advise whether immunophenotyping and molecular studies will be useful.

Differential diagnosis may include parapsoriasis, which some experts say is pre-CTCL. Patients with parapsoriasis should be monitored long-term to determine if it develops into MF, she said. Pathology slides show typical lymphoid infiltrates, Pautrier microabcesses, lymphocytes without spongiosis, vacuolar interface dermatitis, and papillary dermal fibrosis. Staging is important to determine a treatment plan. Additional tests may include lymph node checks, imaging, and labs.

Factors predictive of progression include advanced skin involvement; extracutaneous disease; old age, male gender, African American heritage; large cell transformation; increased lactate dehydrogenase or LDH; and presence of blood tumor clones. For T1 stage, there is no altered life expectancy or risk of progression. For T2 stage, survival is worse with plaque than patches.
While community dermatologists can manage early disease, Dr. Kartono said tertiary care referral is necessary for advanced disease. Clinical trials may be a good option for the latter patients. Treatment requires skin-directed therapies first, then a loop-back mechanism of treatment options. Combination therapy, not monotherapy, is more effective. Supportive care improves the quality of life for CTCL patients.

Among the skin-directed therapies she reviewed were nitrogen mustard, topical steroids, topical bexarotene, tazarotene, imiquimod, localized radiation therapy, and PUVA/UVB. Total skin electron beam therapy is reserved for severe skin symptoms or poor response to other therapies. Systemic therapies include biologic response modifiers, histone deacetylase inhibitors, and chemotherapy, the latter of which is inappropriate as a first-line therapy.

Moving to primary CBCLs, Dr. Kartono noted that it comprises 20% to 25% of all cutaneous lymphomas. They are mostly indolent lymphomas; very different from their systemic/nodal counterparts. Primary CBCLs are confined to the skin at presentation. Be aware that complete staging procedures are often negative for six months after initial workup and no standardized guidelines for care exist. Primary CBCL is classified as indolent, intermediate, and aggressive.

Psoriasis, Psoriatic Arthritis Review

As many as 7.5 million Americans have psoriasis. This common, chronic, inflammatory disease of the skin and joints is considered an autoimmune disease caused by both genetic and environmental influences, stated Robert G. Greenberg, M.D.

Plaque psoriasis is the most common form. Other forms include guttate, pustular, inverse, and erythrodermic. Common locations, which are helpful with the diagnosis, are the scalp, elbows/knees, lower back, navel, and hands/feet. Nail psoriasis is characterized by pitting, peeling, discoloration, lifting up from the nail bed, and ridging.

The current view of psoriasis maintains that the trigger is delivered to draining lymph nodes, which then activate the T-cells. The T-cells move from the lymph nodes into the skin, releasing inflammatory factors, he explained. These factors trigger rapid production of skin cells, widen blood vessels, and stimulate itch nerves.

Papules, plaques, and nodules on the head and neck, extremities, and trunk raise the clinical suspicion for CBCL. To biopsy, go wide and deep, she said, using a 4 to 6 mm punch or excision biopsy. Hematoxylin and cosin stain stain for histology and relevant immunohistochemistry staining should be performed. Proliferation markers will help determine how fast growing it is. If they light up, Dr. Kartono said, then the CBCL should be treated aggressively by an oncologist. It’s important to rule out primary cutaneous marginal zone lymphoma and follicle center lymphoma, both of which present similarly, because CBCLs have a much better prognosis than their nodal counterparts, she added.

Primary CBCL, leg-type, is characterized by rapidly growing red-violaceous tumors. It is common in the elderly with a 5-year survival rate between 35% and 50%. Recommendations for staging evaluation in cutaneous lymphomas other than MF and SS have been published. These patients require a complete history and review of systems, a thorough physical exam, and a specific lab work-up. Imaging may be beneficial if lymph node involvement is suspected. Bone marrow biopsy is optional. Most cases of primary CBCL are caught on imaging, she said, negating the need for bone marrow biopsy.

In summary, Dr. Kortono said that management of cutaneous lymphomas should be driven by symptoms. Local treatment should be used for localized disease. Biologics should be used only when generalized disease is present and symptomatic. Regardless of treatment type, there is an approximate 50% relapse rate post-initial therapy. She cautioned not to over treat indolent cases or under treat aggressive cases.

While the exact cause of psoriasis is unknown, Dr. Greenberg said, triggers may include emotional stress, infection, injury to the skin, weather, and certain drugs. The majority of people with psoriasis feel “angry,” “frustrated,” and “helpless,” according to data from the National Psoriasis Foundation (NPF). The disease negatively impacts patients’ overall wellbeing. Nearly one-third of them have another chronic, inflammatory disease, as well.

While psoriasis requires lifelong treatment, no single treatment works for everyone, he said. Switching therapies is common as is using combination treatments. Dr. Greenberg reviewed a schematic treatment ladder that moves up from topical therapies to light to systemic therapies, depending upon disease severity, noting that he has jumped directly to systemic therapies in certain cases.

Options for localized disease, defined as less than 5% body surface
Neutrophilic Vascular Dermatoses

Neutrophilic dermatoses are inflammatory conditions of the skin often associated with underlying systemic disease. “Think of the skin as the window to the body,” stated Joseph Jorizzo, M.D. As an example, cutaneous lesions on a patient diagnosed with bowel-associated dermatosis-arthritis syndrome imply that the inflammatory bowel disease isn’t being controlled.

Among the neutrophilic dermatoses that he spoke about were Sweet’s syndrome, Behcet’s disease, bowel-associated dermatitis-arthritis syndrome, PG, and LE. While the cutaneous findings in neutrophilic dermatoses vary from vesiculopustules, plaques, and nodules to ulcerations, they all have similar histologic patterns. Therefore, therapeutic approaches can be similar.
Many times, drugs given to treat the underlying disease get blamed for causing neutrophilic vascular reactions. A rheumatologist prescribes MTX for a patient who develops PG three weeks later, saying it was drug-induced. The first thing to ask about with neutrophilic vascular dermatoses is what's going on with the underlying condition and then how is it being treated, he said.

When a patient presents with a complex medical dermatoses, there are three possibilities, Dr. Jorizzo explained. The first is that the clinicopathologic diagnosis integrates all of the findings to determine the underlying disease causing it. In this case, the dermatologist must work with other specialists to determine an appropriate treatment plan for the patient that will address the cutaneous findings as well as the underlying disease. The second possibility is that the clinicopathologic diagnosis reveals a neutrophilic reaction dermatosis, and the dermatologist must communicate with an internist to determine the underlying medical condition. The third possibility, which is the most common, is that there is no direct relationship.

It’s important not to let the patient “drive” the treatment, said Dr. Jorizzo, noting that he could never get a patient to do a gluten-free diet before it became popular on the Internet. “Don’t let the patient talk you into something and then blame you when it doesn’t work.” The patient may have to try 10 different therapies before determining the best one to treat the condition.

Next, Dr. Jorizzo outlined four steps to diagnosing and managing neutrophilic dermatoses. Step 1 is getting the clinicopathologic diagnosis correct. As part of that, it’s important to have a sense of the extent of the disease. Step 2 is to assess the extent of the internal manifestations of the disease. Let the PCP order the necessary tests under your guidance, he said. Step 3 involves assessing for etiology. For a patient with vasculitis who has three episodes a year, a urinalysis should be done after each episode to find out if the vasculitis is affecting the patient’s kidney. Step 4 requires using a therapeutic ladder, setting limits for how high you will go with treatments.

When these steps are not followed, a misdiagnosis can occur. As an example, approximately 20% of the population experience simple aphthous lesions, that is, canker sores. This should not be confused with complex aphthosis, a disorder characterized by recurrent oral and genital aphthous ulcers or almost constant, multiple oral aphthae, but without manifestations of an underlying disease. The latter should not be confused with Behcet’s disease, which has similar symptoms plus arthritis, cutaneous lesions, and ocular, gastrointestinal, and neurologic manifestations. However, patients with complex aphthosis can be misdiagnosed as having Behcet’s disease. Following appropriate steps for patient evaluation and a treatment therapeutic ladder would minimize such misdiagnoses from occurring. The therapeutic ladder for these patients ranges from topical corticosteroids through colchicine and combination colchicine and dapsone therapy to thalidomide.

In general, neutrophilic dermatoses respond to systemic corticosteroids and other immunomodulatory therapies. Sweet’s syndrome can often be effectively treated with a brief course of systemic corticosteroids. However, PG can be recurrent, and early initiation of a steroid-sparing agent is prudent. Second-line treatment for both of these conditions includes medications affecting neutrophil function in addition to immunosuppressant medications. If all else fails, the miracle drug is thalidomide,” he concluded. “It really works.”