Drug-Aggravated Derm Diseases Elude Experts

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STOWE, VT. — Drug-aggravated dermatologic diseases are far more elusive and less common than cutaneous drug reactions, said Dr. Peter W. Heald at a dermatology conference sponsored by the University of Vermont.

To help unmask some of the dermatologic impostors, Dr. Heald, professor of dermatology at Yale University, New Haven, Conn., presented a series of clinical cases from his own practice along with management pearls gleaned from personal experience and recent literature.

Interferon-Induced Cytokine Psoriasis

Cytokine psoriasis—a subset of psoriasis with a unique clinical appearance and therapy profile—started appearing with some frequency around 1990, not coincidentally around the time treatment with interferon for hepatitis C became more common, Dr. Heald said. "Over the past decade, we've started seeing tons of patients who are 1-2 months into interferon therapy coming in with psoriasis that's just gone crazy. They have acute, irritated, oozing lesions, sometimes with pruritus and often associated with palmar lesions and acral dermatitis," he said. Of interest, the psoriatic lesions are not local to the interferon injection sites, but rather are all over the body and, if the patient has or is prone to psoriatic arthritis, that will be induced or aggravated as well.

Although the exact underlying mechanism for this is not fully understood, psoriasis is thought to be an immune-mediated disease with a cytokine profile predominantly of the T helper cell, type 1 (TH1) subset. Presumably, interferon-α triggers psoriasis by activating dendritic cells and T cells involved in the pathogenesis of the condition, according to Dr. Heald. "I'm not a big believer in interferon inducing new cases;" it is more likely that interferon causes problems in people who are prone to psoriasis or who have a mild case, he said. "If you've got a condition where you've already got a TH1-mediated process going on in the skin, and you feed that interferon, it's going to cause problems."

The plan for managing this type of psoriasis is to treat the patients while they are completing their course of interferon therapy. "The usual regimen is etanercept—I start them on 50 mg twice a week—with or without prednisone for rapid onset of relief," Dr. Heald said. "In my experience, the response to etanercept for this type of psoriasis is even better than [it is for] regular psoriasis." At the end of the interferon course, patients can be safely tapered off of the etanercept, he said.

An important consideration in the management of these patients, said Dr. Heald, is to involve the treating physician in the decision process. "Let them know that you are going to start treatment and that you're comfortable using the anti-tumor necrosis factor therapy."

Lithium Psoriasis

"It's not an unusual scenario to see someone on lithium for bipolar disorder getting worsening psoriasis that persists even after 2 months of methotrexate," Dr. Heald said. "Clinically, it's quite similar to interferon-exacerbated psoriasis in that it is tough and doesn't melt away quickly with standard treatments."

While the mechanism for this condition is also not well understood, it is suspected that lithium influences the proinflammatory cytokines in the "psoriatic cytokine network," according to Dr. Heald. As with hepatitis C patients receiving interferon, treating psoriasis in patients on lithium requires treating through the condition with methotrexate or a biologic drug.

A unique management difficulty has to do with the nature of the patient population. "You have to be particularly careful because many of these bipolar patients may be prone to suicide," said Dr. Heald. "If the bipolar patient is at risk for noncompliance or at times has gone out of control, you should be in a situation where you're controlling the modality—whether by having a nurse give [the patient] the methotrexate or biologic agent or by bringing the patient in for infliximab infusions."

ACE Inhibitor Psoriasis

Many individuals with psoriasis take angiotensin-converting enzyme (ACE) inhibitors without incident. In a small subset of patients, however, the antihypertensive medication has been linked to the induction or exacerbation of psoriasis. At one point, ACE inhibitors were associated with an increase in skin kinin levels, but a recent study suggests that the presence in some patients' families of an ACE insertion allele may confer susceptibility to the development of psoriasis and may be the precursor to ACE inhibitor psoriasis exacerbation (Br. J. Dermatol. 2004;151:792-5).

A typical patient with this condition "is someone whose psoriasis has been stable but becomes more widespread and pruritic within 6 months of initiation [of] ACE inhibitor treatment," according to Dr. Heald. "Often there will also be small, thin lesions in places where the patient hadn't had them before."

The best way to determine if ACE inhibitors are linked to worsening psoriasis in a given patient is to ask if the psoriasis got more unruly with dose increases, which would suggest that the ACE inhibitor had a role in the psoriatic process, Dr. Heald said. If you suspect ACE inhibitor involvement, "talk with the patient's internist about switching medications," he said, noting one caveat: "Often the first words out of the internist's mouth are 'let's put them on one of these new angiotensin receptor antagonists,' which may not be a good idea because there has been at least one report linking those to the development of pustular psoriasis."

Because there are alternative antihypertensive medications, it's not necessary to treat the psoriasis through the ACE inhibitor therapy. "It's best to just go off that class of drugs completely," said Dr. Heald. "If after 6 months off [the ACE inhibitor] there's no change in scenario, you can feel comfortable restarting the drug knowing you considered the possibility."

β-Blocker Psoriasis

It's fairly common knowledge that β-blockers have some connection with psoriasis, but there is not a lot of literature to provide insight into the association, Dr. Heald said. "The literature has three scenarios that have occurred with β-blockers and psoriasis—two of which would be hard to miss. One is a psoriasiform drug eruption and the other is conversion to pustular psoriasis within 1 month of starting the drug," he said. The third, less obvious scenario is an insidious worsening of psoriasis over time in the presence of a β-blocker on the medication list.

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DR. HEALD

"There's no blood test that you can do and there are no good guidelines for pursuing [the association]," said Dr. Heald, who recommended running through a list of questions when considering the possibility of β-blocker psoriasis. "If the problem has arisen within 4 months of initiating the drug, you've got to pursue it. But before talking to the patient about an expensive therapy such as [etanercept], you have to ask yourself if you are really just treating what could be taken care of by eliminating just one drug off the medication list," he said. If so, "that should lead you to question whether the risk of the medication for the psoriasis is more or less than the risk of switching away from the β-blocker."

Because there are usually good alternatives for β-blockers in most patients, "I think a 12-week break makes sense," Dr. Heald said. "Most studies show that if resolution is going to happen, it will be within 3 months of stopping the drug. If you recommend this to the patient and his or her [primary care physician] or cardiologist, you insert yourself as being a caring physician, because they know you're looking for a way to treat this without adding on another medication."

Antimalarial Psoriasis

"I recently saw a patient who started on an antimalarial medication to treat symmetric polyarthritis with psoriasis. Within 2 weeks of starting the drug, he began to develop what I call a 'fill in the gap' type of psoriasis, in which erythema develops in between preexisting plaques," Dr. Heald said. "We've seen a bunch of these cases because for a while at our Veterans [Affairs] hospital a patient had to fail an antimalarial before getting approval for treatment with a biologic for psoriatic arthritis." To manage this condition, "we stop the drug immediately and switch over to something that can treat both [psoriasis and psoriatic arthritis] and possibly a prednisone taper," Dr. Heald said. "I don't think psoriasis patients should ever be put on antimalarials. Hydroxychloroquine inhibits epidermal transglutaminase activity, which leads to irregular keratinization and dermoepidermal detachment and cleft formation. In psoriatics, this leads to an erythrodermic form of the disease."

Efalizumab-Interruption Psoriasis

Most dermatologists have legions of happy psoriasis patients thanks to the efficacy of biologics for continuous control of their conditions, "but there is one little side to this that has not been published enough: the possibility of psoriasis exacerbation when treatment is interrupted," said Dr. Heald, who has had patients weeks and even months into successful therapy whose psoriasis returns with a vengeance following two or three missed doses. "One of my patients went on a trip and forgot his medication for 3 days. He experienced an unbelievably quick, abrupt aggravation with lots of very pruritic new lesions and oozing lesions." It's unclear what's behind this, he said, but it's possible that with an interruption in therapy "all those cells go barreling back into the skin and create this abrupt syndrome."

To manage the reaction, "I have sometimes tried getting prednisone or cyclosporine in there right away just to get immediate control because these patients get so bad so quickly, and then [I] start another form of therapy."

Pyoderma Gangrenosum

Although not common, the development of virulent pyoderma gangrenosum–type ulcers at the interferon injection sites of some patients receiving the drug for multiple sclerosis or hepatitis C, "appears to be the result of interferon aggravating one of the TH1 types of inflammatory processes that typically occurs within 3 months of starting the therapy," Dr. Heald said. Biopsies of the affected areas may show neutrophil infiltrates of vasculitis.

"Because patients and their neurologists love the drug, they're not going to stop it, so they will want you to help manage them through it," Dr. Heald said. This is particularly true for patients with multiple sclerosis. "Patients who are staying on interferon for MS can be taught how to do interlesional triamcinolone injections, which I've had the most success with."

Vitiligo and Imiquimod

In some patients, the topical immunomodulator imiquimod can induce local interferon-γ release and vitiligo hypopigmentation. "Probably, in patients prone to vitiligo, the imiquimod triggers an immunomodulating event that may enhance a latent cell-mediated process," Dr. Heald said. "In the patients I've treated with this condition, nobody has developed vitiligo all over. It's been localized to the area of imiquimod application." In terms of treatment, once imiquimod therapy is withdrawn, one of the other topical immunomodulator drugs may play a role, he said. ■