The expanding saga of hydrochlorothiazide and skin cancer

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One of the many challenges that dermatologists confront is recognizing when a patient's systemic medication(s) may be influencing cutaneous disease. Knowing when to discontinue a drug or allow its use is often based on speculation.

Hypertension is the major risk factor for cardiovascular disease worldwide. A systolic blood pressure exceeding 140 mm Hg was estimated to be responsible for 14% of total deaths in 2015.[1] Regarding management, if lifestyle modifications (maintaining normal weight, exercising regularly, and reducing dietary sodium) are insufficient, antihypertensive medications are necessary. First-line antihypertensive drug classes include thiazides, β-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and α-blockers. A recent Cochrane analysis concluded that low-dose thiazides reduced all morbidity and mortality outcomes in adult patients with moderate-to-severe hypertension. First-line ACE inhibitors and calcium channel blockers may be similarly effective, but the evidence is of lower quality.[2] Treatment must be tailored for each hypertensive patient on the basis of the effectiveness and tolerability of the drugs.

In this issue of the *Journal of the American Academy of Dermatology*, Pedersen et al have examined the association between hydrochlorothiazide (HCTZ) use and the risk of Merkel cell carcinoma (MCC) and malignant adnexal skin tumors (MAST). Utilizing Danish nationwide health registries, the authors identified all patients with incident MCC or MAST in 2004-2015 and matched them to cancer-free population controls. They determined that the adjusted odd ratios for MCC and MAST associated with high use (≥50,000 mg) of hydrochlorothiazide were 2.3 and 3.6, respectively, increasing to 3.3 and 5.6 with the highest use (≥100,000 mg). They found no increase in risk of the aforesaid tumors in analyses of other antihypertensive agents, except a tendency toward an increased risk of MCC associated with use of furosemide (odds ratio, 1.9). Their conclusion is that HCTZ use is associated with an increased risk of MCC and MAST.[3]

These authors have previously reported an association between HCTZ and nonmelanoma skin cancer, especially squamous cell carcinoma[4] and melanoma.[5] Other authors have not reached the same conclusion. In their meta-analysis, Gandini et al determined that calcium channel blockers increased nonmelanoma skin cancer risk, with a relative risk of 1.14, and β-blocker users were at increased risk of developing melanoma, with a relative risk of 1.21 There was no association between thiazide diuretic, ACE inhibitor, or angiotensin receptor blocker use and skin cancer risk.[6]

Although these are conflicting data, if you accept the proposition that HCTZ is associated with skin cancer, the presumed carcinogenic pathomechanism for HCTZ is ultraviolet-induced dissociation of its chlorine substituent, leading to free radical formation and DNA damage.[7]

What should dermatologists do with this information? Personally, having had both hypertension and melanoma, I am honestly more concerned with the former than with the latter. Patients and their primary physicians should be cognizant of the current literature, with the understanding that it is not dogma. Fortunately, there are several options available for hypertensive patients who are at high risk of skin cancer to avoid the use of HCTZ, if possible. Discontinuing HCTZ does not diminish the need for routine skin cancer surveillance and sun precautions.

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