Culprits of Medication-Induced Telogen Effluvium, Part 2

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PRACTICE **POINTS**

- Medications are a common culprit of telogen effluvium (TE), and medication-induced TE should be suspected in patients presenting with diffuse nonscarring alopecia who are taking systemic medication(s) such as heparin and its derivatives.
- Infection, illness, or hospitalization around the time of initiation of the suspected culprit medication may complicate identification of the inciting cause and may contribute to TE.
- Angiotensin-converting enzyme inhibitors and β-blockers are unlikely culprits of medication-induced TE, and the benefits of discontinuing a suspected culprit medication should be weighed carefully against the risks of medication cessation.

Telogen effluvium (TE) is a common mechanism underlying medication-related alopecia. The inciting cause of TE may be difficult to identify due to delays in clinically apparent hair loss. Because medication-induced TE is a nonscarring alopecia that typically is reversible, appropriate management requires identification of the underlying trigger and cessation of potential culprit medications. In part 2 of this 2-part series on medication-induced TE, we focus on anticoagulant and antihypertensive medications.

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Medication-induced telogen effluvium (TE) is a nonscarring alopecia that typically is reversible. Appropriate management requires identification of the underlying trigger and cessation of potential culprit medications. In part 2 of this series, we review anticoagulant and antihypertensive medications as potential contributors to TE.

Anticoagulants

Anticoagulants target various parts of the coagulation cascade to prevent clot formation in patients with conditions that increase their risk for thromboembolic events. Common indications for initiating anticoagulant therapy include atrial fibrillation,[1] venous thromboembolism,[2] acute myocardial infarction,[3] malignancy,[4] and hypercoagulable states.[5] Traditional anticoagulants include heparin and warfarin. Heparin is a glycosaminoglycan that exerts its anticoagulant effects through binding with antithrombin, greatly increasing its inactivation of thrombin and factor Xa of the coagulation cascade.[6] Warfarin is a coumarin derivative that inhibits activation of vitamin K, subsequently limiting the function of vitamin K–dependent factors II, VII, IX, and X.[7,8] Watras et al[9] noted that heparin and warfarin were implicated in alopecia as their clinical use became widespread throughout the mid-20th century. Onset of alopecia following the use of heparin or warfarin was reported at 3 weeks to 3 months following medication initiation, with most cases clinically consistent with TE.[9] Heparin and warfarin both have alopecia reported as a potential adverse effect in their structured product labeling documents.[10,11]

Heparin is further classified into unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH); the latter is a heterogeneous group of medications derived from chemical or enzymatic depolymerization

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of UFH.[12] In contrast to UFH, LMWH exerts its anticoagulant effects through inactivation of factor Xa without the ability to bind thrombin.[12] An animal study using anagen-induced mice demonstrated that intraperitoneal administration of heparin inhibited the development of anagen follicles, while in vitro studies showed that the addition of heparin inhibited mouse dermal papilla cell proliferation.[13] Other animal and in vitro studies have examined the inhibitory effects of heparin on signaling pathways in tumor lymphangiogenesis, including the vascular endothelial growth factor C/vascular endothelial growth factor receptor 3 axis.[14,15] Clinically, it has been demonstrated that heparin, especially LMWHs, may be associated with a survival benefit among certain cancer patients,[16,17] with the impact of LMWHs attributed to antimitotic and antimetastatic effects of heparin on tumor growth.[14] It is hypothesized that such antiangiogenic and antimitotic effects also are involved in the pathomechanisms of heparin-induced alopecia.[18]

More recently, the use of direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, and apixaban has increased due to their more favorable adverse-effect profile and minimal monitoring requirements. Bonaldo et al[19] conducted an analysis of reports submitted to the World Health Organization's VigiBase database of alopecia associated with DOACs until May 2, 2018. They found 1316 nonduplicate DOAC-induced cases of alopecia, with rivaroxaban as the most reported drug associated with alopecia development (58.8% [774/1316]). Only 4 cases demonstrated alopecia with DOAC rechallenge, suggesting onset of alopecia may have been unrelated to DOAC use or caused by a different trigger. Among 243 cases with a documented time to onset of alopecia, the median was 28 days, with an interquartile range of 63 days. Because TE most commonly occurs 3 to 4 months after the inciting event or medication trigger, there is little evidence to suggest DOACs as the cause of TE, and the observed cases of alopecia may be attributable to another preceding medical event and/or medication exposure.[19] More studies are needed to examine the impact of anticoagulant medications on the hair cycle.

Antihypertensives

Hypertension is a modifiable risk factor for several cardiovascular diseases.[20] According to the 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease,[21] first-line medications include thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs).

Angiotensin-converting enzyme inhibitors exert their antihypertensive effects by reducing conversion of angiotensin I to angiotensin II, thereby limiting the downstream effects of vasoconstriction as well as sodium and water retention. Given the proven mortality benefit of ACE inhibition in patients with congestive heart failure, ACE inhibitors are used as first-line therapy in these patients.[22,23] Alopecia associated with ACE inhibitors is rare and limited to case reports following their introduction and approval in 1981.[24-28] In one case, a woman in her 60s with congestive heart failure initiated captopril with development of an erythematous pruritic rash on the extremities and diffuse scalp hair loss 2 months later; spontaneous hair growth resumed 1 month following captopril discontinuation.[25] In this case, the hair loss may be secondary to the drug eruption rather than true medication-induced TE. Initiation of enalapril in a woman in her 30s with hypertension was associated with diffuse scalp alopecia 4 weeks later that resolved with cessation of the suspected culprit, enalapril; rechallenge with enalapril several months later reproduced the hair loss.[27] Given limited reports of ACE inhibitor–associated hair loss relative to their pervasive use, a direct causal role between ACE inhibition and TE is unlikely, or it has not been rigorously identified. The structured product labeling for captopril includes alopecia in its list of adverse effects reported in approximately 0.5% to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.[29] Alternative inciting causes of alopecia in patients prescribed ACE inhibitors may include use of other medications, hospitalization, or metabolic derangements related to their underlying cardiac disease.

Although not indicated as a primary treatment for hypertension, β-blockers have US Food and Drug Administration approval for the treatment of certain arrhythmias, hypertension, heart failure, myocardial infarction, hyperthyroidism, and other conditions.[30] β-Blockers are competitive antagonists of β-adrenergic receptors that limit the production of intracellular cyclic adenosine monophosphate, but the mechanism of β-blockers as antihypertensives is unclear.[31] Evidence supporting the role of β-adrenergic antagonists in TE is limited to case reports. Widespread alopecia across the scalp and arms was noted in a man in his 30s several months after starting propranolol.[32] Biopsy of an affected area of the scalp demonstrated an increased number of telogen follicles with no other abnormalities. Near-complete resolution of alopecia was seen 4 months following cessation of propranolol, which recurred within 4 weeks of rechallenge.[32] Although the histopathologic features are compatible with TE, the loss of body hair and rapid recurrence within 4 weeks of rechallenge are atypical for TE. As such, the use of propranolol and the reported alopecia may be coincidental or evidence of an atypical drug reaction distinct from medication-induced TE. Only a handful of other case reports have been published describing TE in patients treated with β-blockers, including metoprolol and propranolol.[33,34] Alopecia has been reported with the use of carvedilol in up to 0.1% of participants.[35] Although cases have been reported, TE appears to be an uncommon occurrence following β-blocker therapy.

Minoxidil—Oral minoxidil originally was approved for use in patients with resistant hypertension, defined as blood pressure elevated above goal despite concurrent use of the maximum dose of 3 classes of antihypertensives.[36] Unlike other antihypertensive medications, minoxidil appears to cause reversible hypertrichosis that affects nearly all patients using oral minoxidil for longer than 1 month.[37] This common adverse effect was a desired outcome in patients affected by hair loss, and a topical formulation of minoxidil was approved for androgenetic alopecia in men and women in 1988 and 1991, respectively.[38] Since its approval, topical minoxidil has been commonly prescribed in the treatment of several types of alopecia, though evidence of its efficacy in the treatment of TE is limited.[39,40] Low-dose oral minoxidil also has been reported to aid hair growth in androgenetic alopecia and TE.[41] Taken orally, minoxidil is converted by sulfotransferases in the liver to minoxidil sulfate, which causes opening of plasma membrane adenosine triphosphate–sensitive potassium channels.[42-44] The subsequent membrane hyperpolarization reduces calcium ion influx, which also reduces cell excitability, and inhibits contraction in vascular smooth muscle cells, which results in the arteriolar vasodilatory and antihypertensive effects of minoxidil.[43,45] The potassium channel–opening effects of minoxidil may underly its hair growth stimulatory action. Unrelated potassium channel openers such as diazoxide and pinacidil also cause hypertrichosis.[46-48] An animal study showed that topical minoxidil, cromakalim (potassium channel opener), and P1075 (pinacidil analog) applied daily to the scalps of balding stump-tailed macaques led to significant increases in hair weight over a 20-week treatment period compared with the vehicle control group ($P<.05$ for minoxidil 100 mM and 250 mM, cromakalim 100 mM, and P1075 100 mM and 250 mM).[50] For minoxidil, this effect on hair growth appears to be dose dependent, as cumulative hair weights for the study period were significantly greater in the 250-mM concentration compared with 100-mM minoxidil ($P<.05$).[49] The potassium channel–opening activity of minoxidil may induce stimulation of microcirculation around hair follicles conducive to hair growth.[50] Other proposed mechanisms for hair growth with minoxidil include effects on keratinocyte and fibroblast cell proliferation,[51-53] collagen synthesis,[52,54] and prostaglandin activity.[44,55]

Final Thoughts

Medication-induced TE is an undesired adverse effect of many commonly used medications, including retinoids, azole antifungals, mood stabilizers, anticoagulants, and antihypertensives. In part 1[56] of this 2-part series, we reviewed the existing literature on hair loss from retinoids, antifungals, and psychotropic medications. Herein, we focused on anticoagulant and antihypertensive medications as potential culprits of TE. Heparin and its derivatives have been associated with development of diffuse alopecia weeks to months after the start of treatment. Alopecia associated with ACE inhibitors and β-blockers has been described only in case reports, suggesting that they may be unlikely causes of TE. In contrast, minoxidil is an antihypertensive that can result in hypertrichosis and is used in the treatment of androgenetic alopecia. It should not be assumed that medications that share an indication or are part of the same medication class would similarly induce TE. The development of diffuse nonscarring alopecia should prompt suspicion for TE and thorough investigation of medications initiated 1 to 6 months prior to onset of clinically apparent alopecia. Suspected culprit medications should be carefully assessed for their likelihood of inducing TE.

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