Received: 1 March 2017 | Accepted: 30 March 2017

DOI: 10.1002/rth2.12001

CASE REPORT

WILEY rpth research and practice in thrombosis and haemostasis | ISTH

Agent specific effects of anticoagulant induced alopecia

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Funding information
Grant support: National Hemophilia Foundation Shire Clinical Fellowship, NIH (R01-HL124232)

Abstract

Alopecia has been observed with many anticoagulants although the mechanism is unclear. A 20 year old female with recurrent DVTs developed alopecia with multiple anticoagulants, including heparin derivatives and the new oral anticoagulants. This resolved with discontinuation of the agents. The patient was ultimately able to be anticoagulated with fondaparinux long term without any alopecia. This case addresses the Key Clinical Question of management and recognition of anticoagulant induced alopecia. This side effect can result from almost any of the available agents and is quickly reversible, underlining the importance of tailoring treatment to the individual and their experiences.

KEYWORDS
adverse effects, alopecia, anticoagulants, fondaparinux, thrombosis

Essentials

- Anticoagulant medications have been known to cause alopecia.
- The reported patient experienced significant alopecia with most anticoagulants.
- Alopecia was quickly reversible.
- Multiple therapeutic trials may be required to identify a tolerable anticoagulant regimen.

1 | CASE REPORT

A 20 year old female with type 2 spinal muscular atrophy, wheelchair dependence, and chronic respiratory failure requiring tracheotomy and ventilator support presented with one day of left lower extremity swelling following prolonged car travel. A duplex venous ultrasound revealed an extensive deep vein thrombosis (DVT) extending from the external iliac to the common peroneal vein. She was started on anticoagulation with enoxaparin (1 mg/kg/dose with anti-Xa activity monitoring to achieve a therapeutic range). One month after initiation of anticoagulation she was seen in the emergency room for worsening symptoms. A repeat ultrasound revealed maturation of her known thrombi but a right lower extremity examination discovered an asymptomatic DVT of the right common femoral vein. Due to a second event while on anticoagulation and her ongoing immobility, the decision was made to continue her on indefinite anticoagulation. Given the potential risk of osteopenia with long term exposure to heparins, and patient preference to avoid laboratory monitoring and injections, she was switched to rivaroxaban (15 mg daily). After initiation of anticoagulation with enoxaparin, the patient had noted mild hair loss. Immediately following the transition to rivaroxaban, she reported a significant increase in diffuse hair loss, and approximately 50% of her total scalp hair-bearing area became hairless within a month of starting the medication. Hair loss was reported to be spontaneous as well as secondary to manipulations, such as brushing. This resulted in significant thinning and multiple bald spots averaging 2 cm in diameter. Due to patient distress regarding the new onset alopecia, she was transitioned to fondaparinux (2.5 mg daily with anti-Xa monitoring). Following this change, she immediately noted less hair loss and over time had complete hair regrowth. Due to preference for an oral anticoagulant, a trial of apixaban (2.5 mg twice daily) was attempted which again resulted in rapid hair loss, resolving upon transition to

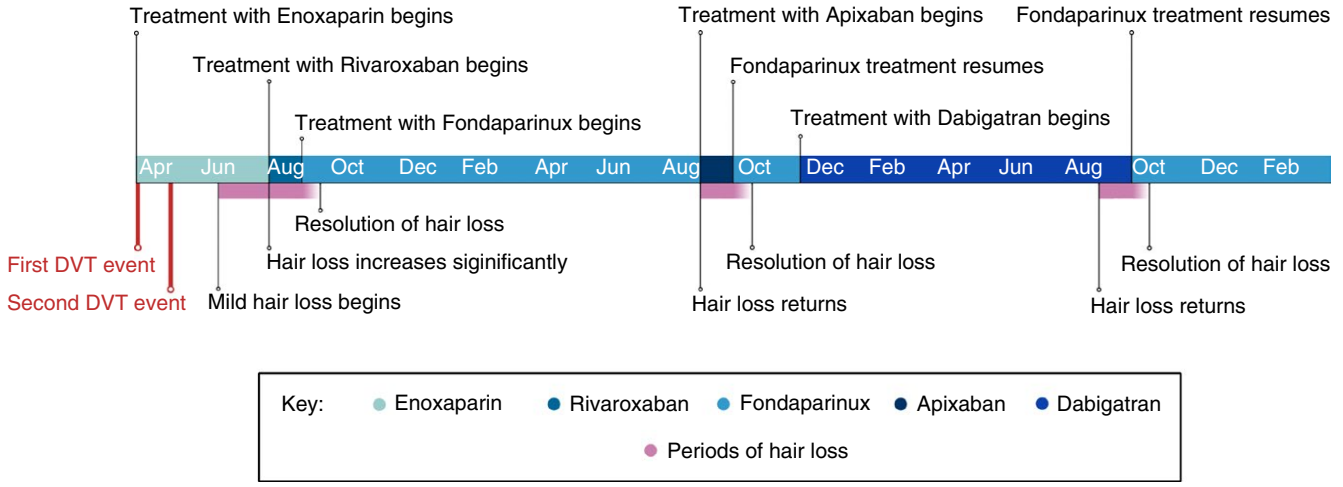

FIGURE 1 Time course of patient's symptoms and medication usage

fondaparinux. Fondaparinux was then replaced with the direct thrombin inhibitor dabigatran (initially 75 mg twice daily, then increased to 150 mg twice daily in order to achieve detectable anti-IIa activity). She tolerated this medication for approximately 10 months before noting a decrease in lower extremity hair growth, followed by return of major spontaneous hair loss from her scalp. At that time her anti-IIa activity was detectable and slightly lower than the previous determination, and her kidney function was unchanged. Given this, she was transitioned back to fondaparinux, which she continues to tolerate without any signs of hair loss (clinical course illustrated in Figure 1).

2 | DISCUSSION

The hair growth cycle is comprised of three stages. The first stage is growth or anagen phase, during which hair grows continuously due to vigorous mitotic activity in the matrix. This typically lasts months to years and the duration of this phase determines the length. This stage is followed by a catagen phase during which the hair matrix cells undergo apoptosis. Growth ceases, there is shortening of the follicle, and mature hair moves upwards toward the scalp where it enters the telogen or rest phase.[1] This final stage lasts approximately 3 months and during this period the hair rests in anticipation of shedding by mechanical forces or replacement by newly growing follicles. Between 85% and 90% of hair at any given time is in the anagen phase with 9-14% in the telogen phase and 1% in the catagen phase. There is significant variability between individuals with regards to the proportion of hair in and length of each phase.[2]

Drug-induced hair loss occurs by two different mechanisms, both of which affect the anagen phase. Anagen effluvium involves abrupt cessation of hair growth through antimitotic activities and is seen with cytotoxic agents such as chemotherapy. Typically, alopecia onset is rapid and anagen hairs fall out within days to weeks of exposure.[1] Alternatively, telogen effluvium results from premature shifting of anagen hair into the catagen phase followed by the telogen phase. The effects are usually seen a few months following a trigger and can be secondary to childbirth, malnutrition, fever, surgery, hemorrhage, as well as pharmaceuticals.[3]

Alopecia during anticoagulation has been described, with heparins and vitamin K antagonists (VKAs) being the most common offenders. Reported incidences range from 30% to 40% with VKAs and 54-66% with unfractionated heparin[4,5] although these numbers seem quite high compared to our center's adult and pediatric clinical experience. Another report describes diffuse alopecia, principally involving the scalp, in 40% of patients on warfarin.[6] It does not appear that age, duration or dosage are risk factors[6] and diffuse, but reversible alopecia usually begins a few weeks after initiation.[6–8] Warfarin does not affect the intermediate (catagen) phase but instead forces follicles to enter the shedding (telogen) phase too early. Based on the timing and presentation of the hair loss reported, it has been proposed that telogen effluvium is the likely process by which alopecia occurs.[9] Loss has been described with the use of rivaroxaban. Findings from the Dresden New Oral Anticoagulant (NOAC) registry report an incidence of 4.4 per 100 patient years,[10] with onset between 22 and 183 days following initiation of treatment in the 12 patients reported. Five cases associated with rivaroxaban

TABLE 1 VigiAccess data on hair loss with anticoagulants

Anticoagulant	Alopecia	Madarosis	Other
Enoxaparin	47	2	7
Warfarin	721	6	249
Rivaroxaban	615	2	60
Fondaparinux	8	1	0
Dabigatran	232	4	24
Apixaban	149	0	12

Data obtained from Vigiaccess.org (referenced March 2017[16]) include reports from 1968 to the present.
Madarosis is loss of eyelashes or eyebrows. Other symptoms include abnormal hair growth, abnormal hair patterns, hair color changes, abnormal hair texture, trichorrhexis (weak points along hair shaft predisposing to breakage).

and one associated with dabigatran were found within the French Pharmacovigilance Database.[11]

Our patient also experienced hair loss following the initiation of rivaroxaban although the symptom occurred rapidly after initiation, more suggestive of anagen effluvium. Heparin is known to possess some antimitotic activity[12] which may support this hypothesis. Other mechanisms may also be involved as heparin has been shown to increase dermal-epidermal cohesion in rats[13] as well as to have inhibitory effects on hair growth.[14] On the adverse drug reaction probability scale developed by Naranjo et al[15] this case scores an 8, making causality highly probable. Further support for causation exists in that hair regrowth occurred with the switch to fondaparinux and loss recurred after the switch to apixaban. Most of the offenders in this report exert their anticoagulant effect through anti-Xa activity, although it is surprising that fondaparinux did not cause hair loss given the common mechanism. One difference is that fondaparinux acts through antithrombin III (although enoxaparin does as well), while rivaroxaban and apixaban bind directly to factor Xa. We therefore selected dabigatran, a direct thrombin inhibitor which resulted in hair regrowth and no signs of alopecia for approximately 10 months. Review of reports of anticoagulant-induced hair loss through VigiAccess demonstrates that all agents can cause multiple symptoms of hair pathology, with alopecia being the most predominant for each one (Table 1, VigiAccess is an online tool which allows users to access Vigibase, the World Health Organization database of suspected adverse reaction reports, which includes more than ten million cases from over 120 countries, from 1968 to the present[16]). To date there are 234 reports of dabigatran associated alopecia, as well as 4 reports of madarosis (loss of eyelashes or eyebrows),[16] so perhaps it is not surprising that this ultimately caused alopecia as well in our patient, despite a long lag time. Interestingly, enoxaparin and fondaparinux had the fewest reports, although this could reflect frequency of usage.[16] Fondaparinux is a very small heparin derivative (a simple pentasaccharide). The common side effects of larger heparins, such as heparin-induced thrombocytopenia and osteopenia are reduced with decreased molecular weight,[17–19] which also might partially explain the differential effects in our patient.

In summary, we have found that anticoagulant-induced alopecia occurs with multiple agents, although the mechanisms remain unclear. We initially hypothesized that this could have been dose-related as levels were monitored while on enoxaparin, fondaparinux, and dabigatran, but not on apixaban and rivaroxaban. However, eventual alopecia following dabigatran suggests that this is not the complete explanation. Additionally, this case demonstrates that the effects are quickly reversible and we were able to find a regimen that served our patient's needs, while avoiding the concerning side effect. Further study is required to determine whether this effect is dose-related, or linked to patient specific factors.

ACKNOWLEDGMENTS

The authors would like to thank Allison Ferguson for figure creation.

AUTHOR CONTRIBUTION

A. C. Weyand reviewed medical records, reviewed the literature and drafted the manuscript. J. A. Shavit initiated case write-up and performed extensive draft editing and revisions.

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How to cite this article: Weyand AC, Shavit JA. Agent specific effects of anticoagulant induced alopecia. *Res Pract Thromb Haemost*. 2017;1:90–92. https://doi.org/10.1002/rth2.12001