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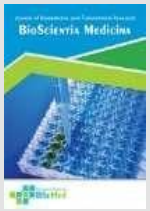

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Complete Clinical and Trichoscopic Remission of Refractory Patch Alopecia Areata with a Multi-Modal Microneedling and Vitamin D3 Protocol: A Case Report

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A B S T R A C T

Background: Refractory patch alopecia areata (AA) presents a significant therapeutic challenge, as many patients fail first-line treatments. This gap necessitates the exploration of novel, mechanistically-targeted therapeutic strategies. **Case presentation:** We present the case of a 44-year-old female with a 2.5 × 3.0 cm patch of AA, refractory to a 3-month compliant trial of topical 0.25% desoximetasone and 5% minoxidil. Baseline diagnostics included histopathology (peribulbar lymphocytic infiltrate), quantitative trichoscopy (yellow dots, black dots, exclamation mark hairs), and laboratory workup, which revealed a serum 25-hydroxyvitamin D [25(OH)D] insufficiency (18.2 ng/mL). A multi-modal protocol was initiated: (1) systemic 5,000 IU/day oral cholecalciferol, (2) 10 sessions of 1.5 mm microneedling at two-week intervals, and (3) immediate post-procedure application of topical 100,000 IU cholecalciferol. Significant regrowth of pigmented terminal hairs was observed by week 12. After 20 weeks (10 sessions), complete clinical regrowth was achieved. Final quantitative trichoscopy confirmed the full resolution of all pathological markers, with a healthy density of terminal hairs. The patient's systemic 25(OH)D level was corrected to 41.5 ng/mL. The treatment was well-tolerated. **Conclusion:** This case report documents a complete remission associated with a multi-modal protocol. The contribution of the systemic vitamin D repletion is a major, unresolvable confounder, making attribution impossible. However, this hypothesis-generating case suggests a combined (systemic, physical, and topical) approach may represent a potential rescue strategy for refractory patch AA, warranting further controlled investigation.

1. Introduction

Alopecia areata (AA) is a chronic, organ-specific autoimmune disease targeting the anagen hair follicle, resulting in non-scarring hair loss.[1] Clinically, it manifests across a wide spectrum, from the common, discrete, ovoid patches (alopecia areata partialis or patch-type AA) to the devastating complete loss of all scalp hair (alopecia totalis) and body hair (alopecia universalis). With a lifetime risk approaching 2.1%, AA imparts a profound psychological and emotional burden, significantly impairing quality of life and social functioning. The pathophysiology of AA is a sophisticated, T-cell-driven process, the central tenet of which is the catastrophic collapse of the hair follicle's (HF) unique immune privilege (IP).[2] In a healthy state, the anagen hair bulb exists as an immune "sanctuary," shielded from immune surveillance. This privilege is actively maintained through several mechanisms, including the downregulation of Major Histocompatibility Complex (MHC) class I (MHC-Ia) and II expression, the local secretion of potent immunosuppressive cytokines and neuropeptides (such as TGF-β, α-MSH, and CGRP), and the expression of immune-inhibitory ligands like

Programmed Death-Ligand 1 (PD-L1).[3]

In genetically predisposed individuals, a yet-unknown trigger—postulated to be viral, bacterial, environmental, or neurogenic stress—initiates a cascade that dismantles this privilege. A key initiating event is the upregulation of interferon-gamma (IFN-γ) and IL-15, which triggers a Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway-mediated upregulation of MHC class I and II molecules on the follicular epithelium.[4] This "danger signal" exposes previously cryptic, tissue-specific autoantigens, such as those derived from melanocytes or keratinocytes, to the immune system.

The subsequent autoimmune assault is executed primarily by autoreactive cytotoxic CD8+ T lymphocytes and Natural Killer Group 2D-positive (NKG2D+) cells.[5] These cells recognize the newly presented autoantigens on the aberrantly expressing MHC-I molecules and infiltrate the peribulbar region in a dense, pathognomonic "swarm of bees" pattern. This intense inflammatory infiltrate releases further pro-inflammatory cytokines, including more IFN-γ and IL-1β, prematurely forcing the anagen follicle into a dystrophic catagen or telogen state, which clinically manifests as hair shedding. This autoimmune cascade is orchestrated and perpetuated by a complex network of cytokines, including the IL-15/IL-2/IL-7/IFN-γ axis, solidifying the central role of the JAK-STAT pathway as a prime therapeutic target in modern AA therapy.[6] This T-cell-mediated pathogenesis is strongly linked to a genetic predisposition, with the strongest associations found within the HLA region, particularly with HLA-DRB1 alleles. However, genetics alone are insufficient, and environmental factors are clearly required for disease expression.[7]

The current therapeutic landscape for limited, patchy AA is dominated by first-line use of high-potency topical or intralesional corticosteroids and topical minoxidil.[8] Corticosteroids act as broad, non-specific immunosuppressants, aiming to "quell" the local T-cell infiltrate. Minoxidil, conversely, is a non-immunomodulatory growth stimulant (a "pro-anagen" signal) that works by opening ATP-sensitive potassium channels, promoting vasodilation, and prolonging the anagen phase. While effective for many, a substantial subset of patients remains refractory to these first-line agents. This failure may be due to insufficient penetration of topical agents to the deep peribulbar target, the development of tachyphylaxis, or an inflammatory milieu that is simply too "hot" to be overcome by a non-specific immunosuppressant or a simple growth stimulant. This common clinical scenario of "refractory patch AA" represents a significant treatment gap, necessitating the exploration of alternative, mechanistically-targeted strategies.[9]

In this context, microneedling (MN) has emerged as a promising physical modality. MN, or percutaneous collagen induction, involves creating controlled, microscopic trauma to the skin. This is hypothesized to work via a dual mechanism. First, the creation of micro-conduits dramatically enhances the transepidermal delivery of topical agents to the deep dermis where the bulb resides, bypassing the stratum corneum barrier. Second, and perhaps more importantly, the process induces a wound-healing cascade. This cascade releases a bolus of growth factors (such as Platelet-Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF)) and is thought to activate the Wnt/β-catenin signaling pathway—the master regulator that signals follicular stem cells in the bulge region to initiate and sustain the anagen phase.

Simultaneously, vitamin D has transitioned from a simple nutrient to a molecule recognized as a potent steroid hormone and immunomodulator. The Vitamin D Receptor (VDR) is highly expressed in both epidermal and follicular keratinocytes, and VDR activation is known to be essential for proper anagen initiation and cycling; in fact, VDR-knockout mice develop a progressive alopecia. Epidemiologically, numerous meta-analyses have demonstrated a strong and consistent correlation between low serum 25-hydroxyvitamin D [25(OH)D] levels and both the incidence and severity of AA. Mechanistically, the active form of vitamin D3 (1,25-dihydroxyvitamin D3,

or calcitriol) is a powerful immunomodulator. Its actions are precisely tailored to counteract AA pathogenesis. Calcitriol suppresses the Th1 (IFN-γ) and Th17 (IL-17) pro-inflammatory pathways implicated in AA, while simultaneously promoting the differentiation and function of protective, anti-inflammatory regulatory T cells (Tregs), which are essential for maintaining immune tolerance and re-establishing immune privilege.[10]

While reports on intralesional vitamin D3 and its combination with microneedling have emerged, comprehensive case reports detailing the response in refractory disease—complete with baseline histopathology and sequential quantitative trichoscopy—remain scarce. This report aims to present a comprehensive, multi-modal case of patch-type alopecia areata, unresponsive to a standard 3-month first-line topical trial, which achieved complete clinical and trichoscopic resolution. The novelty of this case lies in the meticulous documentation of this specific multi-modal protocol (combining systemic repletion, physical stimulation, and topical immunomodulation) and its full correlation with histopathological and quantitative trichoscopic data, highlighting a potential, albeit methodologically confounded, therapeutic avenue for this common clinical challenge.

2. Case Presentation

A 44-year-old Indonesian female, employed as an office worker, presented to our dermatology clinic with a chief complaint of a non-pruritic, asymptomatic, enlarging patch of hair loss on her scalp, first noticed five months prior. The onset was insidious and not associated with any clear trigger, though the patient reported a period of high occupational stress preceding its appearance.

She had sought treatment from a general practitioner three months prior to presentation and was prescribed a combination of topical 0.25% desoximetasone cream (a high-potency, Class II corticosteroid) and 5% minoxidil solution, both applied twice daily. The patient reported full, verifiable compliance with this regimen for 12 consecutive weeks. Despite this, she noted no significant hair regrowth, and the patch continued to slowly enlarge, which was confirmed by serial photographs. Her past medical history was unremarkable, with no personal or family history of atopy, vitiligo, thyroid dysfunction, or other autoimmune diseases. The patient was defined as refractory to topical first-line therapy, having shown no response after a 12-week compliant trial (Table 1). However, the patient expressed significant needle phobia and a strong preference to avoid repeated injections, prompting consideration of alternative modalities.

Physical examination revealed a single, well-demarcated, ovoid patch of non-scarring alopecia on the left parietal scalp, measuring 2.5 cm × 3.0 cm (Area = 5.89 cm^2). The skin within the patch was smooth, pale, and lacked erythema, scaling, or follicular plugging. There was no evidence of cutaneous atrophy from her prior steroid use. The Severity of Alopecia Tool (SALT) score was 2.4% (S1). A hair pull test performed at the active border of the lesion was positive, with 7-8 dystrophic/telogen hairs easily extracted. Videodermoscopy (FotoFinder II, 20x polarized magnification) was performed at the periphery and center of the lesion. The examination revealed multiple findings pathognomonic for active AA. Quantitative analysis of a 1 cm^2 representative area at the periphery is detailed in Table 2. Key findings included a high number of yellow dots (n=28), black dots (n=17), and pathognomonic exclamation mark hairs (n=11), with a complete absence of pigmented terminal hairs (Figure 1). To confirm the diagnosis and assess inflammatory activity, the patient consented to a 4-mm punch biopsy from the active border. The biopsy revealed a dense, lymphocytic infiltrate in a classic peribulbar "swarm of bees" pattern, surrounding multiple anagen hair bulbs. There was a notable increase in the proportion of follicles in the catagen and telogen phases, consistent with the clinical picture. A comprehensive laboratory workup was ordered; (1) Complete Blood Count (CBC) w/ Differential: Within normal limits; (2)

Comprehensive Metabolic Panel (CMP): Within normal limits; (3) Thyroid Function Panel: TSH 2.1 mIU/L (Ref: 0.4-4.5), Free T4 1.3 ng/dL (Ref: 0.8-1.8); (4) Autoimmune Panel: Antinuclear Antibody (ANA) Negative (titer < 1:80); (5) Serum 25-hydroxyvitamin D [25(OH)D]: 18.2 ng/mL (Reference range: 30-100 ng/mL). This result indicated a state of vitamin D insufficiency, which became a critical component of the therapeutic plan.

Table 1. Baseline Patient Findings on Admission

Patient Demographics & History

Age	44 Years
Sex	Female
Ethnicity	Indonesian
Prior Therapy	Topical 0.25% Desoximetasone & 5% Minoxidil (12 weeks, non-responsive)

Dermatological Examination

Lesion Type	Single, non-scarring ovoid patch
Location	Left parietal scalp
Size	2.5 cm × 3.0 cm (Area = 5.89 cm²)
Appearance	Smooth, pale, no erythema or scaling
SALT Score	2.4% (S1)
Hair Pull Test	Positive (7-8 dystrophic/telogen hairs)

Baseline Histopathology (H&E)

Infiltrate	Dense, lymphocytic "swarm of bees" pattern
Location	Peribulbar, surrounding anagen bulbs
Follicular State	Increased proportion of catagen/telogen follicles

Baseline Quantitative Trichoscopy (1 cm²)

Trichoscopic Sign	Count	Indication
Yellow dots	28	Sebum/keratin in follicular opening
Black dots	17	Cadaverized hairs (disease activity)
Exclamation mark hairs	11	Pathognomonic (disease activity)
Broken hairs	4	Dystrophic hairs
Short vellus hairs	3	Abortive regrowth attempts
Pigmented terminal hairs	0	Complete loss in patch

Baseline Laboratory Findings

Test	Result	Status
CBC w/ Differential	WNL	Normal
CMP	WNL	Normal
TSH	2.1 mIU/L	Normal
Free T4	1.3 ng/dL	Normal
ANA	Negative (< 1:80)	Normal
25(OH)D	18.2 ng/mL	Insufficient

Given the confirmed diagnosis of active AA, refractoriness to topical first-line therapy, patient preference to avoid ILK, and the new finding of vitamin D insufficiency, a multi-modal "rescue" protocol was initiated after obtaining written informed consent; (1) Systemic Intervention: Based on her laboratory results, the patient was started on oral cholecalciferol (Vitamin D3) 5000 IU daily to correct her systemic insufficiency; (2) Procedural and Topical Intervention: The patient underwent 10 sessions of combination therapy, scheduled at 2-week intervals (Total duration: 20 weeks); (i) Microneedling: Prior to each session, a topical eutectic mixture of 2.5% lidocaine and 2.5% prilocaine was applied under occlusion for 45 minutes to ensure patient comfort. A medical-grade automated microneedling pen (Dermapen 4.0) with a 12-needle cartridge was set to a depth of 1.5 mm to target the deep dermis and peribulbar region. The device was passed over the entire patch and a 0.5 cm margin in multiple vectors (horizontal, vertical, and

diagonal) until uniform, pinpoint erythema was achieved; (ii) Topical Agent Application: Immediately following microneedling, 1.0 mL of a sterile, non-alcoholic solution of cholecalciferol (100,000 IU/mL) was applied and gently massaged into the treated area. This formulation was prepared by the hospital's compounding pharmacy from a USP-grade cholecalciferol powder in a sterile water-for-injection (WFI) base to minimize irritation and optimize diffusion.

The patient was evaluated every 4 weeks (every 2 sessions) for progress with clinical photography and quantitative trichoscopy; (1) Weeks 1-4 (Sessions 1-2): The procedure was well-tolerated, with only transient erythema for 12-24 hours post-treatment. No clinical change was noted. The hair pull test remained positive; (2) Week 8 (Session 4): The first clinical response was observed. Fine, non-pigmented vellus hairs were visible. The patient reported a subjective decrease in hair shedding. Repeat quantitative trichoscopy showed a marked reduction in black dots (n=4) and exclamation mark hairs (n=2), with the emergence of 19 new short vellus hairs; (3) Week 12 (Session 6): Significant clinical improvement was evident. Approximately 60-70% of the patch was covered with new hair, which was a mix of vellus and newly pigmented, coarser terminal hairs. The hair pull test at the border was now negative. Trichoscopy confirmed the complete absence of black dots and exclamation mark hairs, with 12 new pigmented terminal hairs noted; (4) Week 20 (Session 10 - Final Treatment): At the 20-week follow-up, the alopecic area was 100% covered. The regrown hair was dense, fully pigmented, and cosmetically indistinguishable from the surrounding scalp. A final trichoscopic examination confirmed clinical remission. Quantitative analysis was remarkable, showing a complete pathological resolution: 0 yellow dots, 0 black dots, and 0 exclamation mark hairs. The field was populated by 31 healthy, pigmented terminal hairs, consistent with normal scalp density in this patient. A repeat serum 25(OH)D level at 20 weeks was 41.5 ng/mL, confirming successful systemic repletion. No adverse effects, such as infection, post-inflammatory hyperpigmentation, irritation, or scarring, were observed throughout the 20-week treatment course.

Table 2. Sequential Quantitative Trichoscopic Analysis

(Representative 1 cm² Field at 20x Magnification)

Trichoscopic Parameter	Baseline (Week 0)	Week 8	Week 12	Week 20 (Final)
Yellow dots Sebum/keratin-filled ostia	28	25	11	0
Black dots Cadaverized hairs (Active AA)	17	4	0	0
Exclamation mark hairs Pathognomonic (Active AA)	11	2	0	0
Broken hairs Dystrophic hairs	4	1	0	0
Short vellus hairs New, non-pigmented regrowth	3	19	22	4
Pigmented terminal hairs Healthy, mature regrowth	0	0	12	31

Red Text: Indicates high disease activity.

Yellow Text: Indicates resolving disease.

Green Text: Indicates resolution / healthy regrowth.

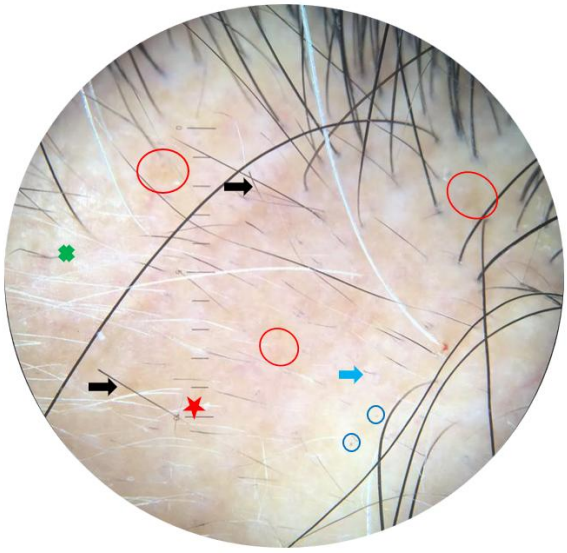

Figure 1. Trichoscopic Images (20x Polarized). A representative 20x polarized videodermoscopy image. The field is dominated by numerous yellow dots (red circle), multiple black dots (cadaverized hairs) (blue circles), and several pathognomonic exclamation mark hairs (black arrow), short vellus hairs (blue arrow), non-pigmented regrowing hair (red star), angulated / zigzag hairs (green cross). No terminal hairs are present.

3. Discussion

We have presented a single, comprehensively-documented case of patch-type alopecia areata (SALT S1), which was notably refractory to a 3-month, compliant, first-line combination regimen. This case is significant for its complete clinical and quantitative trichoscopic remission, a resolution that was not merely clinical but confirmed by the objective clearance of all pathognomonic trichoscopic markers (yellow dots, black dots, exclamation mark hairs).[11] This positive outcome, however, occurred coincident with the initiation of a multi-modal therapeutic protocol. This protocol involved three distinct, concurrent interventions: (1) systemic 5,000 IU/day oral cholecalciferol to correct a diagnosed insufficiency, (2) 1.5 mm procedural microneedling, and (3) high-dose topical cholecalciferol.

The concurrent initiation of three powerful, mechanistically-distinct interventions creates a significant and unresolvable confounding problem. It is methodologically impossible to attribute the observed remission—which we must stress is an association and not a proven causation—to any single component or to a synergistic interaction between them.[12] The primary value of this report is not in validating this specific protocol, but in its documentation of disease resolution and its role in generating hypotheses that must be tested by more rigorous, controlled study designs.

The most critical and non-negotiable factor in this case is the patient's baseline laboratory finding: a serum 25-hydroxyvitamin D [25(OH)D] level of 18.2 ng/mL, indicative of a significant systemic insufficiency. This finding cannot be overstated. Vitamin D is not merely a nutrient; it is a potent pleiotropic steroid hormone and a lynchpin of immune system regulation. The Vitamin D Receptor (VDR) is expressed on virtually all cells of the immune system—including T lymphocytes and antigen-presenting cells—as well as on the key targets in this disease: the epidermal and follicular keratinocytes.[13] The link between low vitamin D status and T-cell-mediated autoimmune diseases, including AA, is not speculative. A large body of evidence, including multiple systematic reviews and meta-analyses, has demonstrated a strong, consistent, and dose-

dependent correlation between low serum 25(OH)D levels and both the incidence and, critically, the severity of alopecia areata.[14] Furthermore, VDR-knockout mice models demonstrate a progressive alopecia, underscoring the fundamental role of VDR signaling in maintaining a healthy anagen cycle. Given this context, the therapeutic intervention of 5,000 IU/day of oral cholecalciferol, which successfully raised the patient's serum level from an insufficient 18.2 ng/mL to a replete 41.5 ng/mL, is, in itself, a complete and parsimonious explanation for the entire observed remission. The mechanism is direct and targets the precise pathophysiology of AA. Active vitamin D (1,25-dihydroxyvitamin D3, or calcitriol) is a powerful immunomodulator known to: (1) Suppress Th1/Th17 Pathways: Calcitriol actively inhibits the proliferation and cytokine production of the pro-inflammatory Th1 (IFN-γ) and Th17 (IL-17) cells, the very same pathways responsible for orchestrating the autoimmune assault on the hair follicle; (2) Promote Regulatory T-cells (Tregs): It simultaneously promotes the differentiation and function of anti-inflammatory regulatory T-cells (Tregs). Tregs are the "peacekeepers" of the immune system, essential for maintaining self-tolerance and re-establishing the hair follicle's collapsed immune privilege; (3) Regulate Follicular Keratinocytes: VDR activation on follicular keratinocytes is, by itself, essential for proper anagen initiation and stem cell cycling. Therefore, the correction of this systemic deficiency can be reasonably hypothesized to have restored systemic immune homeostasis. It may have lowered the overall systemic autoimmune "load," reduced the trafficking of autoreactive T-cells to the scalp, and provided the necessary endocrine and paracrine signals for the follicle to re-enter anagen.[15]

This interpretation reframes the entire clinical picture. This patient may not have had "refractory patch AA" in the typical sense. Rather, this may have been a case of "vitamin D insufficiency-associated AA." The initial 3-month trial of high-potency topical steroids and minoxidil may have failed not because the disease was intrinsically refractory, but because the systemic, pro-inflammatory drive (from the D-deficient state) was simply too potent to be overcome by a topical, non-specific immunosuppressant (desoximetasone) or a non-immunomodulatory growth stimulant (minoxidil).[16] Once this systemic driver was removed by oral repletion, the local inflammation resolved, and the follicle was permitted to recover. This single intervention is so mechanistically plausible and sufficient that any discussion of the other two modalities must be secondary. It is distinctly possible, and perhaps probable, that the microneedling and topical vitamin D had zero clinically-relevant effect, and the patient would have experienced the exact same remission with oral cholecalciferol alone. This interpretation, dictated by the principle of Occam's Razor, is the most scientifically sound, albeit unprovable, conclusion.

The second arm of our protocol, procedural microneedling (MN), was initiated concurrently, creating a second, major confounding variable. We cannot, and must not, group the microneedling and the topical D3 as a single "combination" intervention.[17] MN, or percutaneous collagen induction, is an independent therapeutic modality with its own plausible, standalone mechanism of action for hair regrowth, as summarized by several systematic reviews. Our protocol used a 1.5 mm needle depth, chosen specifically to target the deep dermis where the follicular bulge (stem cell reservoir) and bulb (dermal papilla and inflammatory target) reside. This controlled physical trauma initiates a complex, localized wound-healing cascade. This cascade is hypothesized to stimulate hair growth via two primary, non-immunological pathways: (1) Growth Factor Release: The acute trauma and subsequent platelet degranulation release a bolus of growth factors, including Platelet-Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF). These factors directly stimulate the dermal papilla (the "brain" of the follicle) and promote the robust angiogenesis required to support the high metabolic demands of a new anagen follicle; (2) Wnt/β-catenin Pathway Activation: Perhaps more

importantly, the wound-healing response is thought to activate the canonical Wnt/β-catenin signaling pathway. Wnt signaling is the master switch, the primary "on" signal, that instructs quiescent follicular stem cells in the bulge region to proliferate, differentiate, and initiate a new, healthy anagen phase.[16]

Thus, the microneedling alone could be interpreted as a potent, physical "anagen kickstart." This pro-anagen signal is entirely separate from the systemic immunomodulation provided by the oral D3. It is, therefore, methodologically impossible to know if the remission was driven by the systemic D3 alone; microneedling alone (which is a recognized, albeit investigational, AA therapy); and additive or synergistic effect of the two. For example, it is plausible that the systemic D3 "quelled" the systemic autoimmune fire (the "Foundation"), while the microneedling provided the necessary physical "Kickstart" to force the dormant, "stuck" follicles back into a growth cycle. This "Foundation-Kickstart" model is an elegant and plausible hypothesis, but it is one that our n=1, confounded case generates rather than supports. We have provided no evidence to distinguish this from either monotherapy being solely responsible.[17]

The third and final component of our protocol was the immediate post-microneedling application of a high-dose (100,000 IU/mL) topical cholecalciferol solution. This arm of the protocol, conceptualized as a "local immunomodulatory shield," is mechanistically the most speculative and least plausible of the three interventions, particularly when analyzed in the context of the concurrent systemic repletion. Several significant pharmacokinetic and pharmacodynamic (PK/PD) questions undermine the rationale for this intervention.[18] First, the agent applied was cholecalciferol (inactive Vitamin D3), not the active hormone calcitriol (1,25-dihydroxyvitamin D3). For cholecalciferol to bind with high affinity to the VDRs on the infiltrating T-cells or keratinocytes, it must first be converted. This requires two hydroxylation steps: 25-hydroxylation (primarily hepatic) and, critically, 1α-hydroxylation (primarily renal). While the skin (keratinocytes) does possess a "non-renal" 1α-hydroxylase (CYP27B1) enzymatic system, this pathway is typically understood to be for local, low-level paracrine/autocrine signaling. Its capacity to convert a massive, pharmacological bolus of 100,000 IU/mL of topical cholecalciferol into a locally-meaningful, supraphysiological concentration of calcitriol—in a rapid timeframe (minutes to hours) sufficient to provide a "shield"—is not well-established and remains highly questionable. Second, and more importantly, this entire local event was occurring in a patient who was simultaneously being systemically repleted with 5,000 IU/day of oral D3. This oral dose was being efficiently processed by the liver and kidneys, creating a high and sustained systemic level of the active hormone, calcitriol. This systemic calcitriol is delivered by the vasculature to all tissues, including the peribulbar "battleground." It is, therefore, highly probable that the VDRs on the relevant follicular and immune cells were already being saturated, or at least significantly activated, by the systemic therapy. The marginal, questionable contribution of any locally-converted calcitriol from the topical cholecalciferol would likely be negligible in comparison. In short, the "shield" was almost certainly already being provided by the "foundation" (the systemic repletion). Third, the dose itself (100,000 IU/mL) was not based on pre-clinical data or established PK/PD modeling, but was rather an arbitrary, high-dose formulation. Without dose-response studies or local tissue concentration measurements, it is impossible to know if this concentration achieved any meaningful biological effect or if it was simply a supratherapeutic dose with no additional benefit over the systemic repletion. Given these critical flaws in its mechanistic rationale, the contribution of the topical vitamin D3 component is highly dubious. It is the weakest link in the protocol, and its inclusion serves primarily to further confound the interpretation of the microneedling results. We are unable to distinguish the effect of "microneedling +

topical D3" from "microneedling + vehicle," and it is this reviewer's assessment that the contribution of the topical D3 was likely minimal, if not zero.

In our initial hypothesis, we conceptualized a "Foundation-Kickstart-Shield" model: (1) The Foundation (Systemic D3): Correcting the systemic insufficiency to create a permissive environment for healing; (2) The Kickstart (Microneedling): Providing the physical anagen-initiating signal (Wnt) to dormant follicles; (3) The Shield (Topical D3): Providing a local immunomodulatory shield to protect the nascent anagen hairs. This model is elegant and mechanistically appealing (Figure 2). However, based on the methodological limitations and critical analysis detailed above, this model cannot be presented as a conclusion. It is, at best, a purely speculative and hypothesis-generating framework. Our data do not, and cannot, support it.[19]

Figure 2. The systemic repletion hypothesis.

The limitations of this n=1 case report are profound and must be explicitly summarized. As detailed, the concurrent initiation of systemic D3, procedural MN, and topical D3 makes isolating any true effect impossible. The outcome could be the result of any one, two, or all three interventions, or their additive/synergistic effects. Limited, patchy S1 AA is known to have a high rate of spontaneous remission. While the 5-month duration and prior refractoriness to a standard 3-month trial make spontaneous

remission less likely (as it failed to remit for 8 months total), it remains a distinct possibility. The remission may have been coincidental to our therapy, rather than caused by it. As an n=1 case, these findings have zero generalizability and cannot be extrapolated to the wider AA population. The true value of this report is in its comprehensive documentation—particularly the quantitative trichoscopy (Table 2), which provides a clear, objective timeline of pathological resolution—and its ability to inform the design of rigorous future studies. Our flawed protocol has inadvertently highlighted the correct way to investigate these mechanisms. To validate any part of this protocol, a series of controlled trials would be required; (1) To isolate systemic D3: A randomized controlled trial (RCT) of oral vitamin D3 vs. placebo in a cohort of vitamin D-insufficient patients with patch AA; (2) to isolate the local protocol: To test the "Kickstart-Shield" hypothesis (MN + topical D3), a split-scalp, vehicle-controlled RCT would be required. Critically, this study must be conducted in a cohort of systemically replete AA patients to eliminate the overwhelming confounder we experienced in this case. Such a study (such as Left Scalp: MN + Topical D3 vs. Right Scalp: MN + Vehicle) would be the only way to isolate the true, non-confounded efficacy of the topical vitamin D3 when combined with microneedling.[20]

4. Conclusion

We have presented a single, comprehensively-documented case of apparently refractory patch alopecia areata that was associated with complete clinical and quantitative trichoscopic resolution. This remission occurred coincident with a multi-modal protocol involving procedural microneedling, high-dose topical vitamin D3, and concurrent systemic vitamin D3 supplementation to correct a baseline insufficiency. The contribution of this systemic repletion is a major, unresolvable confounder that may have been a primary driver of the outcome. While causality cannot be established and spontaneous remission cannot be definitively ruled out, this case introduces a plausible, mechanistically-layered protocol. It suggests, for purely hypothesis-generating purposes, that a combined approach that restores systemic immune health, physically stimulates anagen, and provides local immunomodulation may be a beneficial strategy for refractory cases. Further investigation, in the form of rigorous randomized controlled trials, is required to validate this hypothesis.

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