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Letter to Editor

Role of Ki67 Proliferative Index in Various Alopecia – A Pilot Study

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Dear Editor,

Diffuse alopecia presents significant challenges in dermatology, especially in women. Its main causes – female androgenetic alopecia (AGA), chronic telogen effluvium and diffuse alopecia areata (AA) – can exhibit similar signs, complicating diagnosis. Telogen effluvium typically occurs 2–3 months after triggers like childbirth or surgery, though triggers may be unclear. Early-stage AGA and diffuse AA can lack obvious signs, further complicating diagnosis. When clinical evaluation is difficult, tools such as trichoscopy, scalp biopsy and immunohistochemistry can help differentiate these conditions. Immunohistochemical techniques are increasingly valuable in diagnosing various skin disorders.

The Ki-67 protein was first identified using a monoclonal antibody developed from Hodgkin lymphoma cell line L428.[1] Ki67 is a nuclear protein that indicates cellular proliferation, predominantly expressed during the anagen phase of hair follicles, reflecting active regeneration.[2] Increased Ki67 levels are associated with hair growth, allowing researchers to differentiate between types of alopecia, such as AGA and telogen effluvium, where elevated levels suggest active growth and lower levels indicate disrupted hair cycling.

In AGA, reduced Ki67 expression in hair follicles indicates decreased proliferation and impaired anagen activation, resulting in thinner hair. In telogen effluvium, Ki67 serves as a marker for recovery, with higher levels suggesting a return to the anagen phase. AA shows diminished Ki67 binding, indicating suppressed keratinocyte proliferation.[3] In discoid lupus erythematosus, T-lymphocytic infiltrate affects hair follicles, with apoptotic keratinocytes exhibiting abnormal Ki67, p53 and bcl-2 expression.[4] In addition, Ki67 serves as a biomarker for evaluating treatment efficacy in hair loss therapies. Investigating Ki67 enhances our understanding of hair follicle biology and may lead to targeted therapies for hair regeneration, making it a valuable tool in both clinical and research contexts.

In this cross-sectional pilot study, we collected scalp biopsies from patients with hair disorders – AGA, telogen effluvium, AA, lichen planopilaris and discoid lupus erythematosus (diagnosed clinically and with biopsy) – over 2 months, alongside control subjects. Inclusion criteria required a diagnosis confirmed by biopsy, adults above 18 years, informed consent and no recent treatments (e.g. corticosteroids) which affect hair growth for 3 months before enrolment. Exclusion criteria included other dermatological conditions affecting hair growth, hair restoration surgeries, infections of scalp, pregnancy, lactation and non-compliance. After ethics approval, scalp biopsies from 30 patients were fixed, paraffin-embedded, cut into 3–4 μm sections, stained with hematoxylin and eosin for routine histopathological examination and subjected to Ki67 immunohistochemistry using heat-induced epitope retrieval to assess Ki67 positivity in the outer root sheath of hair follicles.[3]

Table 1: Age distribution.

Age group (10-year interval)	No. of patients	Percentage
15–25	5	16.66
26–35	14	46.66
36–45	7	23.33
46–55	4	13.33
Total	30	100

Table 2: Comparison of the mean Ki-67 immunoreactive cells per hair follicle in each section across different disorders, along with their respective standard deviations.

Disorder	Mean Ki-67 Immunoreactive cells per follicle in each section	Standard deviation
Control	33.8	4.48
Alopecia areata	17.8	2.66
Chronic telogen effluvium	10.8	1.96
Androgenetic alopecia	4.3	1.67
Lichen planopilaris	1.5	1.07
Discoid lupus erythematosus	1	0.95

A total of 30 patients aged 15–55 years participated in the study, with a mean age of 33.6 ± 9.84 years; the most common age group was 26–35 years [Table 1]. Among the participants, 16 were male (56.6%) and 14 were female (43.4%). The mean number of Ki67-immunoreactive cells per hair follicle for each group was as follows: Control group: 33.8 ± 4.48, AA: 17.8 ± 2.6, chronic telogen effluvium: 10.8 ± 1.96, AGA: 4.3 ± 1.67, lichen planopilaris: 1.5 ± 1.07 and discoid lupus erythematosus: 1 ± 0.95 [Table 2]. Analysis of variance (ANOVA) analysis showed a significant difference in the mean number of Ki67-immunoreactive cells among the six groups ($P = 0.00001$).

In our study, Ki-67 immunoreactivity was noted in the outer layer of hair follicles, especially at the hair bulb. Diseased scalp follicles had significantly lower Ki67 levels than controls, with telogen effluvium at 10.8 ± 1.96 cells and AGA at 4.3 ± 1.67 cells. AGA showed lower Ki-67 positivity than chronic telogen effluvium, while discoid lupus erythematosus and lichen planopilaris had the least. ANOVA revealed significant differences in Ki67 levels among the six groups ($P = 0.00001$), highlighting its potential to differentiate hair disorders based on proliferation.

Ashrafuzzaman *et al.* reported a significant decrease in Ki-67-immunoreactive cells in AA and AGA compared to controls, indicating reduced proliferative activity.[5] Our study found similar decreases in Ki67 positivity. Van Baar *et al.* also noted reduced Ki-67 binding in anagen hair follicles in AA, emphasizing its role in assessing hair follicle proliferation.[3]

Limitations include a small sample size that may limit generalizability, high costs of Ki-67 immunohistochemical analyses hindering larger studies and variability in staining techniques that can affect measurement accuracy and reproducibility.

This study compared the growth fraction in keratinocyte populations of normal and diseased hair follicles using Ki67. We found subtle differences in proliferation among disorders, especially between AGA and chronic telogen effluvium. While Ki67 provides insights into proliferation, its utility in distinguishing specific disorders may be limited. Larger studies are needed to validate these findings and explore additional markers for improved diagnostic accuracy and management of hair disorders. Further research is essential to assess the clinical utility of Ki67 immunohistochemistry.

Ethical approval: The research/study approved by the Institutional Review Board at ASRAMS BHR Ethics Committee, number ASRAMS BHR-EC/Approval No. 165/2023, dated 25 August 2023.
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