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Diffuse Alopecia: Clinical, Trichoscopic, Histopathological and Immunohistochemical challenges in the Diagnosis

Thesis

*Submitted for Partial Fulfillment of Master Degree in **Dermatology and Verology***

By

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Aisha Bashir Sheikh Adan

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List of Abbreviations

Abb.	Full term
5αR	5-reductase
AA	Alopecia areata
AAI	Alopecia areata incognita
AGA	Androgenetic alopecia
APC	Antigen-presenting cell
BMP	Bone morphogenetic protein
DAA	Diffuse alopecia areata
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DP	Dermal papilla
FAA	Female androgenetic alopecia
FPHL	Female patten hair loss
HDAC9	Histone deacetylase 9
HFs	Hair follicles
IRS	Inner root sheath
LPP	Like lichen planopilaris
MHC	Major histocompatibility complex
MIF	Migration inhibitory factor
NK	Natural killer
ORS	Outer root sheath
SD	Standard deviation
SPSS	Statistical package for Social Science
TE	Telogen effluvium
VIP	Vasoactive intestinal peptide

INTRODUCTION

Diffuse hair shedding is a common complaint and a major challenge in the practice of dermatology, especially when it affects women. Female-pattern hair loss (FPHL), telogen effluvium (TE), and diffuse alopecia areata incognita (AAI) are its three main causes. It is often difficult to distinguish one from the other, and clinical data, laboratory findings, physical examination, procedures, and biopsy may be needed for a definitive diagnosis ***(Werner and Brenner, 2012).***

Alopecia areata incognita (AAI) has been first described by **Rebora in 1987.** It is a subtype of alopecia areata, characterized by an acute intense and diffuse hair loss without the typical patches of alopecia. AAI is more common in patients under the age of 40, especially in those from 20 to 40 years of age with a typical strong female predominance. It shares clinical features with telogen effluvium, and it could also be misdiagnosed as androgenetic alopecia. Thus, a scalp biopsy is often required to confirm the clinical diagnosis ***(Tosti et al., 2008).***

The histopathologic findings of AAI may be similar to the classical forms of the disease; however, the findings may be subtle and vary according to the disease stage ***(Jameel et al., 2008).*** The most consistent finding in acute AAI scalp biopsies is an inflammatory infiltrate around the terminal hair bulb. This infiltrates gradually decreases with chronicity and concentrates

around either only the miniaturized follicles or the follicular stelae (streamers) ***(Whiting, 2003).***

Additionally, a reversal in the anagen-telogen and terminal vellus ratios is always observed and maybe the only evidence suggesting the diagnosis in long-standing cases. Thus, from a pathological point of view, AAI should be suspected when high percentages of telogen hairs and/or miniaturized hairs are present even in the absence of a peribulbar lymphocytic infiltrate. The presence of a subtle lymphocytic infiltrate around miniaturized hairs in the papillary dermis strongly suggests the diagnosis ***(Tosti et al., 2008).*** These infiltrates may be present within the empty follicular fibrous tracts (stela), even without a concomitant peribulbar infiltrate ***(Kolivras and Thompson, 2016). Miteva et al. (2012)*** suggested that the main histopathologic clues for AA incognito include the presence of dilated infundibular openings and small basaloid aggregates of cells with round, irregular or polygonal shape, lack of hair shaft and no apoptosis in the outer root sheath, corresponding to small telogen follicles.

Videodermoscopy of hair and scalp is gaining popularity as a valuable tool in the differential diagnosis of hair loss. This method allows viewing of the hair and scalp at X70 to X160 magnifications ***(Rudnicka et al., 2008).***

Since trichoscopy has become an important tool for diagnosis of various hair problems, it has been used also for

diagnosis of AAI from its mimickers. ***Tosti et al. (2008)*** examined 70 cases with AAI with videodermoscopy and found that the presence of numerous yellow dots and short re-growing hairs was a constant feature among AAI patients. Other features less frequently observed were the presence of dystrophic hairs, exclamation point hairs, and cadaverized hair. ***Elghblawi (2016)*** also supported the constant observation of numerous diffuse yellow dots of different size and uniform colors within the follicular orifices as an important feature in AAI. However, ***Rakowska et al. (2009)*** didn't share the same opinion and they found through analysis of different cases of alopecia that the presence of yellow dots in the ''androgen-dependent'' frontal area is the strongest criterion for female pattern androgenetic alopecia. In alopecia areata, yellow dots were less frequent and usually visible in long-lasting, not active alopecia, accompanied by cadaverized, dystrophic, or exclamation mark hairs.

The histological examination of sectioning will allow the detection of follicular pathology, even if it is focal. Moreover, it will yield quantitative data of follicular cycling, as well as morphometric evaluation of the hair follicles throughout their entire length, from the bulb to the acroinfundibulum. To achieve this, a 4-mm punch biopsy specimen including subcutaneous tissue is required ***(Stefanato, 2010).*** The vertical sections demonstrated the full thickness of the skin from the stratum corneum to deep subcutaneous fat in every section. However, they demonstrate only a few hairs in every section.

Any histological study requiring accurate vellus hair count and terminal vellus hair ratio requires the use of the transverse section ***(Garcia and Poletti, 2007).***

The vertical sectioning is believed to be superior to horizontal sectioning and sufficient for routine diagnostic purposes ***(Rakowska et al., 2009).*** Irrespective of whichever level of transverse sectioning of the punch biopsy specimen is chosen, the ultimate goal is to reach the isthmic area. This is the site where the follicular units reside and afford the greatest number of diagnostic findings, including the opportunity to perform accurate follicular counts and follicular ratios ***(Stefanato, 2010).***

The presence of T lymphocytes within the mononuclear infiltrate present AA is already well documented. ***Kolivras and Thompson in 2016*** investigated the possibility to differentiate cases of diffuse alopecia areata from pattern hair loss via immunohistochemical studying of CD3+ infiltrating T cells and found that the presence of CD3(+) lymphocytes within empty follicular fibrous tracts (stela), even without a concomitant peribulbar infiltrate, is a reliable histopathological clue in supporting a diagnosis of AA.

Kamyab et al. (2019) confirmed this finding and demonstrated that among four immunohistochemical markers (CD3, CD4, CD8, and CD20), CD3 is the most specific and sensitive test for differentiating of AA from androgenic alopecia.

In the view that AAI may mimic other disorders with acute diffuse hair shedding including female pattern hair loss (FPHL), telogen effluvium (TE) and the diagnosis of AAI represents a great challenge to identify, we will focus in this study on detection of clinical, trichoscopic, histopathological as well as immunohistochemical analysis for CD3 for analysis of cases with acute diffuse hair loss in females.

AIM OF THE WORK

We aimed to study the clinical, trichoscopic findings, histopathological in patients with acute diffuse hair shedding. Cases with a clinical or trichoscopic diagnosis of female pattern hair loss (FPHL), acute telogen effluvium (TE) and alopecia areata incognita (AAI) would be included. Immunohistochemistry analysis for CD3 would be done for possible differentiation between the three entities.