Clinical Cases in Dermatology
Series Editor: Robert A. Norman

Shannon C. Trotter
Suchita Sampath *Editors*

Clinical Cases in Alopecia

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Clinical Cases in Dermatology

Series Editor
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Clinical Cases in Alopecia

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ISSN 2730-6178 ISSN 2730-6186 (electronic)
Clinical Cases in Dermatology
ISBN 978-3-031-15819-3 ISBN 978-3-031-15820-9 (eBook)
https://doi.org/10.1007/978-3-031-15820-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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63-Year-Old Female with Diffuse Thinning of the Hair

1

Amber Castellanos, Kristina Kazimir, Suchita Sampath, and Shannon C. Trotter

Abstract

Androgenetic alopecia (AGA) is a form of non-scarring alopecia caused by an excessive response to androgens. It is the most common type of progressive hair loss in both men and women, affecting up to 80% of men and 50% of women over the course of their life. Presentations of AGA differ between sexes with men initially experiencing recession of the frontal hairline and increased loss in the temporal regions. In women, the hair loss consists of diffuse thinning at the crown with a presenting concern of a widening center hair part. AGA is a hormonally driven hair loss where androgens may have a paradoxical effect on some areas of the scalp and cause dark terminal hair follicles to regress to fine and colorless vellus hairs. Not only do androgens cause hair follicle regression into vellus hairs, but they also shorten the anagen (growth) phase. This results in a smaller anagen-to-telogen ratio and ultimately leads to follicular shrinkage and a decrease in overall hair coverage on the scalp. Diagnosis of AGA is based on a thorough history and physical exam. Biopsy is rarely required for diagnosis but if performed, shows pronounced miniaturization of hair follicles and complete zones of replacement of terminal hair by vellus hair. Treatment of AGA focuses on increasing scalp coverage as well as impeding the progression of hair thinning. This can be achieved through the use of topical minoxidil for both men and women. The use of oral finasteride may be utilized in men and recent studies suggest its use in non-reproductive females. Females may also use oral spironolactone as an alternative therapy to finasteride. Recent studies are investigating

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_1

the use of platelet-rich plasma, low-level laser therapy, and janus-kinase inhibitors for the treatment of AGA with promising preliminary results.

Keywords

Androgenetic alopecia · Follicular miniaturization · Minoxidil · Finasteride

A 58-year-old female presented with diffuse thinning of her hair on the scalp. She reported gradual thinning of her hair over the past 5 years. Of note, her family history was significant for hair loss with her father and paternal grandfather. She denied hair loss of the eyebrows, eyelashes, or other body hair.

On physical examination, diffuse non-scarring alopecia was noted with retention of hair on the frontal scalp line (Figs. 1.1 and 1.2). Eyelashes and eyebrows appeared

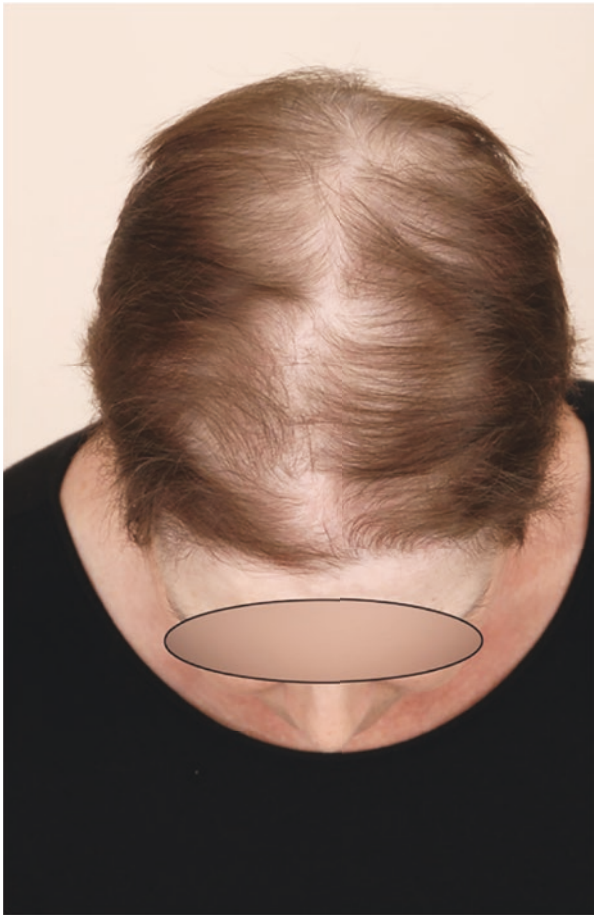

Fig. 1.1 Diffuse thinning of the scalp with widening of the mid-line part. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

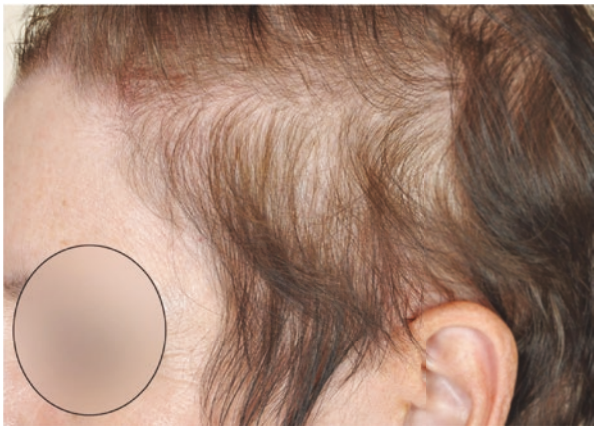

Fig. 1.2 Diffuse thinning of the scalp with retention of the frontal scalp line. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

intact. A scalp biopsy was performed and revealed miniaturization of the hair follicles. Fingernails were normal in appearance.

Based on the clinical case description, what is the most likely diagnosis?

1. Diffuse alopecia areata
2. Drug-induced alopecia
3. Androgenetic alopecia
4. Telogen effluvium

Diagnosis

Androgenetic alopecia.

Discussion

Androgenetic alopecia (AGA) is a form of non-scarring alopecia caused by an excessive response to androgens [1]. This progressive type of hair loss is common in both men and women, affecting up to 80% of men and 50% of women over the course of their lifetime [2]. Although prevalence data is limited, AGA is most prevalent in Caucasian populations, as up 50% of Caucasian men will have AGA by age 50 [3]. Asian and African populations also have high prevalence rates but to a lesser degree when compared to Caucasian populations [4].

Presentations of AGA differ between sexes with men initially experiencing recession of the frontal hairline and increased loss in the temporal regions. This may be accompanied by hair loss at the vertex creating a characteristic "horseshoe" pattern [5] (Fig. 1.3). In women, the pattern of hair loss is not as distinct as in men; it generally consists of diffuse thinning at the crown with a presenting concern of a widening center hair part [6] (Fig. 1.4).

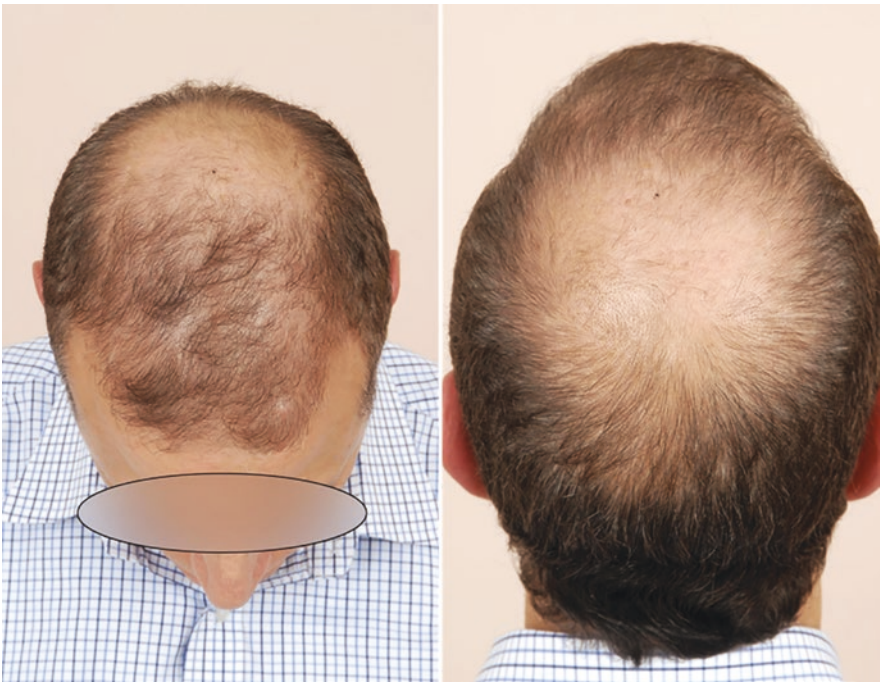

Fig. 1.3 Presentation of AGA in males with recession of the frontal hairline as well as hair loss at the vertex, creating a "horseshoe" pattern. Images courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

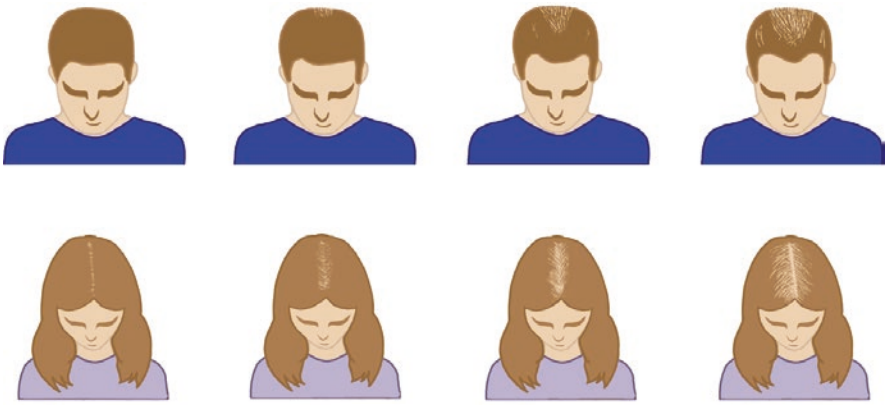

Fig. 1.4 Comparison of the differing presentations of AGA between men and women. The top panel depicts the hair loss pattern seen in men with recession of the frontal hairline and increased loss in the temporal regions. The bottom panel illustrates the diffuse thinning at the crown and widening center part found in women with AGA

Predisposition to AGA is likely multifactorial caused by the interaction of several genes and environmental factors with the risk of developing AGA dramatically increasing when there is a positive family history [7, 8].

As the name suggests, AGA is driven by androgens. Androgens are important regulators of human hair growth. Under baseline conditions, androgens stimulate thin hairs that lack pigment, vellus follicles, to transform into thicker, pigmented, terminal hair follicles [9]. This stimulation of hair growth is most evident during adrenarche when circulating levels of androgens increase resulting in the manifestation of pubic and axillary hair in both sexes. These androgen-stimulated hairs are unlike the terminal hairs found on your head, eyelashes, and eyebrows that can grow constitutively in the absence of androgens [10]. In those with AGA, androgens may have a paradoxical effect on some areas of the scalp and cause dark terminal hair follicles to regress to fine and colorless vellus hairs. This phenomenon is believed to be a result of an imbalance of androgen production and degradation, as well as an increase in the number of androgen receptors [11, 12].

The androgens, dihydrotestosterone (DHT), and nuclear lipophilic enzyme, 5α-reductase are thought to play an important role in the pathophysiology of AGA. In humans, DHT is made from testosterone via the enzyme, 5α-reductase [13, 14]. 5α-reductase has two isoforms (Type I and Type II) in scalp hair follicles [13, 14]. Type II 5α-reductase is a chief mediator of DHT production in the scalp, as it contributes to 80% of DHT production from testosterone [15]. Studies have demonstrated that men with AGA have amplified expression of Type II 5α-reductase and consequently elevated concentrations of DHT and androgen receptors [15]. This proves to be the crux of the pathology of AGA, as DHT and 5α-reductase cause a reduction in hair follicles by shortening certain phases of the hair follicle growth cycle [16, 17]. Normally, hair follicles undergo continual phases of growth and development (anagen), regression (catagen), and rest (telogen), but in those with AGA, the anagen phase is shortened. This results in a smaller anagen-to-telogen ratio and ultimately leads to follicular shrinkage and a decrease in overall hair coverage on the scalp [14] (Fig. 1.5).

The diagnosis of AGA is usually made from the history and clinical findings alone. A thorough history should be elicited to rule out other potential causes of hair loss. The physical exam findings are also imperative for the diagnosis of AGA. The pattern of hair loss described above as well as a negative hair-pull test would suggest AGA instead of telogen effluvium [18]. In women, a complete hormonal evaluation may not be necessary if other signs of androgen excess are not present such as menstrual irregularities, hirsutism, severe cystic acne, virilization, or galactorrhea [19]. If a scalp biopsy is required, the morphological changes are subtle and vary with the stage of AGA. In the early phases, there is a mononuclear inflammatory infiltrate centered at the junction of the follicular infundibulum and the associated sebaceous duct [5]. As AGA progresses, terminal hairs become replaced by vellus or rudimentary anagen hair follicles [5]. Areas of the scalp with well-established androgenetic alopecia show pronounced miniaturization of hair follicles and complete zones of terminal hair replacement by vellus hairs [5].

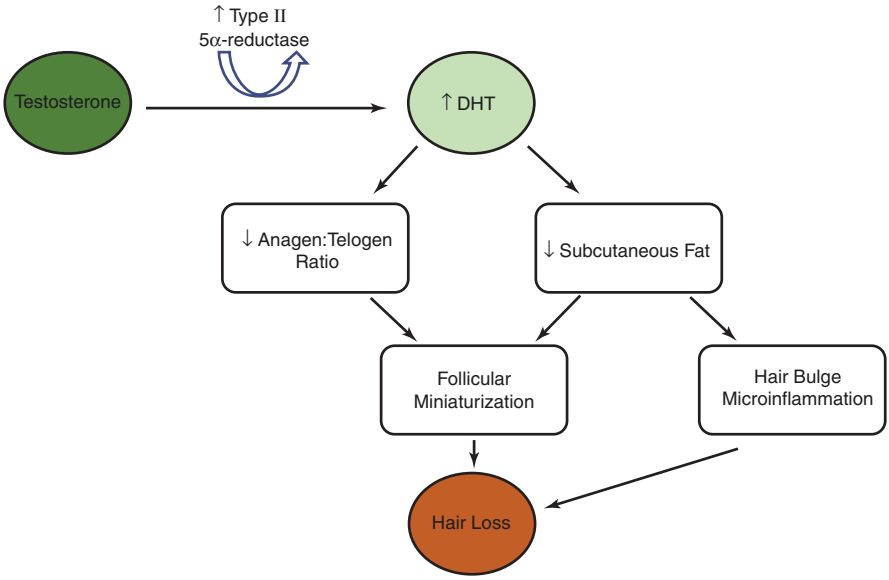

Fig. 1.5 The multiple effects DHT has on hair follicles: Testosterone is converted into DHT by Type II 5α-reductase. In individuals with AGA, there are increased levels of the Type II isoform of 5α-reductase resulting in elevated levels of DHT. DHT, in turn, erodes the subcutaneous fat. Additionally, DHT shortens the duration of the hair growth cycle. The lack of subcutaneous fat and shortened hair cycle prevents hair follicles from growing to their full size. The hair shaft is eventually lost after multiple cycles of hair follicle miniaturization

Treatment

AGA may have a dramatic psychosocial impact and therapeutic intervention may be desired to assist the patient. The goal of AGA treatment is to increase hair growth and impede the progression of hair thinning.

Minoxidil has been a reputable treatment for AGA for over 30 years. Although knowledge of the entire mechanism of action has not yet been elucidated, conversion of minoxidil to its active derivative minoxidil sulphate by follicular sulfotransferase is key to minoxidil's effectiveness. Animal studies have demonstrated that with topical application, minoxidil results in hair follicles remaining in the anagen phase for a longer duration as well as reducing the time spent in the telogen phase [20]. Side effects associated with topical application of either the 2% or 5% formulation of minoxidil are dermatitis, headaches, and hypertrichosis [21]. Another pitfall with topical minoxidil is compliance as peak efficacy is achieved with consistent application of the product. Oftentimes, premature discontinuation of treatment occurs due to a lack of perceived efficacy, adverse effects, or altered hair texture. As a result, a 2019 study compared the efficacy of oral and topical minoxidil in the treatment of female-pattern hair loss. Groups were treated with either 1 mg of oral minoxidil or 5% topical minoxidil solution for 24 weeks. The results showed that

low-dose oral minoxidil provides improvement with female-pattern hair loss, but the results did not differ from topical minoxidil 5% solution [21].

Another highly-regarded treatment option for AGA is the use of oral finasteride, which exerts its effects on Type II 5-alpha-reductase by inhibiting the conversion of testosterone to DHT. Finasteride at a 1 mg dose was approved by the FDA for men with AGA in the late 1990s and has shown great potential for the treatment of female pattern hair loss [16]. It is important to note that despite finasteride's potential teratogenic effect in women of childbearing potential, recent publications have demonstrated positive findings of increased hair density in pre- and post-menopausal women who are not at risk of these side effects [22]. Finasteride only inhibits Type II 5α-reductase while dutasteride, another 5α-reductase inhibitor, blocks both Type I and Type II isoforms [15, 16]. Studies have shown that dutasteride has superior efficacy compared to its predecessor finasteride in promoting hair growth [23].

In women, oral antiandrogens such as spironolactone are often used to treat AGA. Spironolactone, a potassium-sparing diuretic, is also a weak partial agonist to the androgen receptor. Through the weak partial agonist action, spironolactone blocks the more potent DHT and free testosterone from interacting with the androgen receptor [24]. Additionally, spironolactone inhibits androgen synthesis and enhances the conversion of testosterone to estradiol [24].

Other medications such as ketoconazole 2% shampoo demonstrate positive findings in the treatment of AGA, but it is not currently FDA approved for its use [25]. In combination with oral finasteride, this antifungal has been shown to increase hair density and the amount of anagen hair follicles in those with AGA by blocking the production of testosterone [26].

Platelet-rich plasma (PRP) and low-level laser therapy (LLLT) have also exhibited positive potential in treatment for those with AGA [27, 28]. PRP is a non-invasive treatment where a patient's blood is collected in the office and centrifuged to separate platelet-rich plasma. The plasma is then re-injected into an area of target treatment or applied through a microneedling technique. LLLT is considered less invasive as it uses laser light to encourage hair follicle growth [29]. There are several FDA-approved LLLT devices for AGA including: HairMax Lasercomb, Capillus Pro, and iGrow Hair Growth System. All these devices assist in hair regrowth via the stimulation of mitochondrial hair follicle stem cells [29, 30].

Currently, there are investigations into the use of Janus kinase (JAK) signal inhibitors for alopecia areata with promising results. As a result, researchers are hypothesizing similar results with AGA [31]. Further studies into the use and efficacy of PRP, LLLT, and JAK inhibitors would need to be conducted to determine their efficacy and role in the treatment of AGA.

Key Points

- Current research suggests increased androgen receptors and imbalanced androgen production/degradation is responsible for the pathology seen in AGA.

- Finasteride, in combination with topical minoxidil, are first-line, FDA-approved treatment for men with AGA while women may use topical minoxidil in combination with oral spironolactone.
- Topical ketoconazole, while not FDA-approved, has shown promising effects in the phenotypic appearance of those with AGA when used in combination with finasteride.
- Platelet-rich plasma (PRP) has recently gained popularity as an effective treatment for AGA.
- Recent clinical trials of JAK inhibitors demonstrate potential for hair regrowth in AGA.

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58-Year-Old Female with Diffuse Thinning of the Hair

2

Sean Kirk, Amber Castellanos, Suchita Sampath, and Shannon C. Trotter

Abstract

Telogen effluvium is one of the most common causes of non-scarring hair loss. It is triggered by stressful stimuli and often resolves once the stressor is removed or has ended. Generally, there is diffuse loss of hair across the scalp, but it can be more prominent around the temporal, frontal, and occipital areas. In addition to a thorough history, a physical exam with a hair pull test can be implemented for diagnosis. There are several theories about the pathogenesis of telogen effluvium, and although the exact process is unknown, each theory aims to explain the shift and preference toward the telogen phase of the hair growth cycle. The commonality of known causes of telogen effluvium is the patient's encounter with a stressful stimulus. Important aspects of treating telogen effluvium include isolating the precipitating factor and removing or treating it, emphasizing that recovery of hair density will occur as it does not result in entire or permanent hair loss, and providing support services especially if psychological stressors are a central contributory factor. Topical minoxidil is not indicated for the treatment of telogen effluvium but is sometimes implemented by providers. Novel treatments, such as the compound ALRV5XR, yield promising results for patients with telogen effluvium.

Keywords

Telogen effluvium · Non-cicatricial · Alopecia · Stress-induced · Diffuse · Hair pull test · COVID-19

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_2

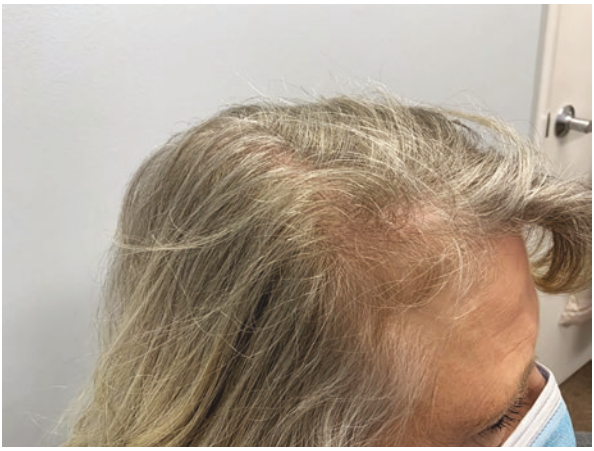

Fig. 2.1 Diffuse thinning with shorter hairs along the frontal scalp line

A 58-year-old female presented with sudden, diffuse thinning of her hair on the scalp. She stated that her hair loss started about ten weeks after she was hospitalized for an infection with the Sars-CoV-2 virus. She brought a plastic bag full of hair to her visit for evaluation.

On physical examination, diffuse non-scarring thinning was noted with short hairs of normal thickness along the frontal scalp line (Fig. 2.1). Eyelashes and eyebrows appeared intact. A hair pull test was positive. Fingernails did not show any abnormalities.

Based on the clinical case description, what is the most likely diagnosis?

1. Diffuse alopecia areata
2. Anagen effluvium
3. Androgenetic alopecia
4. Telogen effluvium

Diagnosis

Telogen Effluvium.

Discussion

Telogen effluvium (TE) is one of the most common causes of non-scarring hair loss. It is triggered by physical or emotional stressful stimuli and generally resolves once the stressor is removed or has ended [1] (Fig. 2.2). Unfortunately, despite being a common cause of hair loss, there is limited epidemiological data on telogen effluvium. For TE, there is no clear difference in the prevalence between males and females, however, females present for assessment more often [2]. Similarly, it is

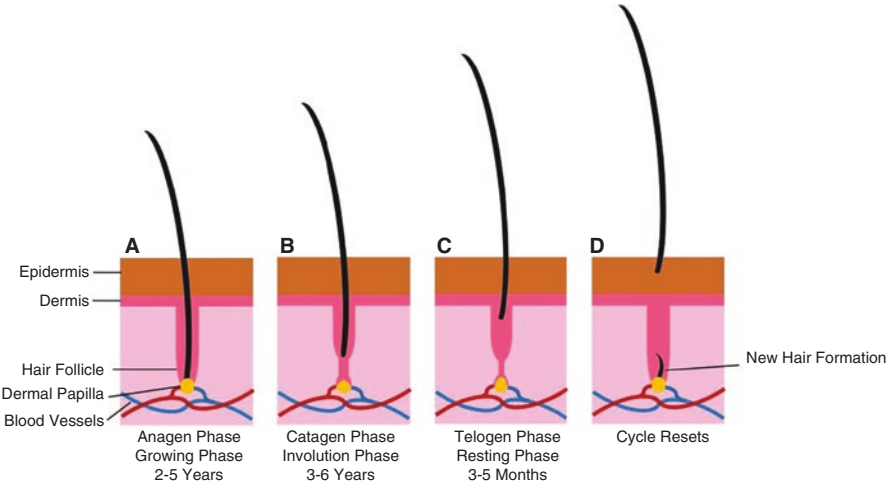

Fig. 2.2 The hair growth cycle: (**a**) Anagen phase: Period of epithelial proliferation where the follicle reaches its maximal length and volume. (**b**) Catagen phase: Period of involution where the lower portion of the follicle involutes via apoptosis. (**c**) Telogen Phase: Marks the period between follicular regression and the onset of the next anagen phase. (**d**) Cycle resets: Beginning of the next anagen phase with new hair growth

unknown if there is a difference in prevalence across racial demographics. Although, a recent study demonstrated that during the COVID-19 pandemic, there was an increase in the incidence of TE in Hispanic/Latinx and other non-white populations with little change in the incidence in black and white populations [3]. This study was limited and further highlights the need to expand the epidemiological understanding of TE.

Telogen effluvium presents as a diffuse loss of hair across the scalp, but hair loss may be more prominent around the temporal, frontal, and occipital areas [1, 4]. Patients with denser hair at baseline may be more difficult to diagnose with TE using only visual appearance at an initial visit. Therefore, a thorough history and previous pictures of the patient can be crucial in the diagnosis of TE in more nuanced cases. Patients bringing in the hair lost during a short period of time can also provide context when they present with typical hair density [1]. Another tool that can be implemented for diagnosis is the hair pull test. To conduct this test, the practitioner should separate approximately fifty to sixty hairs and slowly, but firmly apply traction, then count any removed hairs. A positive hair pull test is when more than 10% of the total pulled hairs are removed and is supportive of the presence of TE [5]. Histopathological evaluation may also be utilized to support the diagnosis of TE and in early disease shows an increased telogen-to-anagen ratio (>20%). Occasionally, increased numbers of catagen follicles and empty follicular tracts may also be seen. If sampled after thinning has already taken place, a biopsy would show a lack of telogen hairs and nearly all the hairs present would be anagen phase hairs [6].

During the process of TE, there can be greater than 25% of the scalp hairs in the telogen phase but it is typically expected to be less than 50% [7, 8]. There are several theories about the pathogenesis of TE. Although the exact mechanism is unknown, each theory aims to explain the shift of hair follicles from the anagen (growth phase) to the telogen phase (shedding phase). One proposed mechanism is immediate anagen release where a stimulus forces a higher proportion of anagen hairs into the telogen phase all at once. Another theory is delayed anagen release where hairs are held in the anagen phase for a prolonged time by a stimulus, and when that stimulus is lost, a larger proportion of hairs enter telogen phase. This mechanism is considered to be involved in postpartum TE [6].

The commonality of known causes of TE is the patient's encounter with a stressful stimulus that can be physical or emotional in nature. Following the triggering event, hair loss from telogen effluvium usually occurs within 2–4 months. Acute or chronic illnesses, surgery, infection, childbirth, nutritional deficiencies, drugs, and emotional situations are common precipitating factors in TE [5]. A recent small study noted an increase in TE cases several months after the beginning of the COVID-19 pandemic [3]. Moreover, another study found that TE, related to COVID-19, presented as a more rapid and robust loss of hair [9]. Although the exact cause for this finding is unknown, either the Sars-CoV-2 infection or the collective psychological stress of the pandemic may be contributory factors consistent with stressful stimuli causing TE.

TE can also occur as a chronic variant, whereby hair loss continues for longer than 6 months. It can result from similar triggers that precipitate acute TE, but the etiology that leads to a more persistent disease is unknown. Chronic TE is often diagnosed in females ages 30–50, and hair loss is most predominant along the frontal and temporal hairlines [10].

Treatment

One of the most important aspects of treating TE is isolating the precipitating factor and removing or treating it. For example, if the suspected cause is a specific medication, the appropriate treatment would be to discontinue it. Similarly, if an underlying chronic disease were present, treating the condition would be the main course of action. Another essential aspect of treatment is educating the patient on the clinical course of TE. It is important to emphasize that the recovery of hair density may take up to a year and that TE will not result in entire or permanent hair loss [11]. Support services may also be a valuable resource for patients when psychological stressors are suspected to be a central contributory factor to the hair loss [12]. In any case, hair loss can be a stressful experience for patients and ensuring that they have a strong support system can be instrumental to further reducing a patient's stress.

Topical minoxidil is not FDA-approved for the treatment of TE but is sometimes implemented as therapy. One small retrospective study showed an improvement in hair loss with oral minoxidil in patients with chronic TE [10]. However, this was a

limited study and further inquiry into the treatment of TE with minoxidil is needed to understand its efficacy.

Recently, an investigation of a novel supplement yielded promising results for patients with TE. The compound of interest, ALRV5XR, is a multi-molecular agent aimed at restoring the normal biological homeostasis of the hair follicle. It is composed of specific compounds obtained from standardized botanical extracts, vitamins, and minerals and was administered orally and topically as a conditioner, shampoo, and follicle serum to increase the delivery of the compound. The study consisted of a cohort of female subjects and measured the terminal hair regrowth over a 24-week period in both placebo and treatment groups. The treatment was well-tolerated and showed a statistically significant increase in the terminal hair regrowth compared with the placebo group [13]. This supplement is available commercially and as it is listed as a "dietary supplement" has not been approved by the United States Food and Drug Administration.

Key Points

- Telogen effluvium (TE) is a non-scarring alopecia that is diffuse and self-limited.
- Precipitating factors can include a wide variety of stressors such as physical and psychological illness, infections, surgery, childbirth, and medications.
- Multiple theories about the exact mechanism of TE have been proposed but the precise mechanism is unknown.
- The primary treatment for TE is identifying and resolving the underlying stressor as well as patient education on the self-limited disease course.

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22-Year-Old Male with Several Discrete Patches of Hair Loss

3

Brittany Snyder, Francesca Veon, Suchita Sampath, and Shannon C. Trotter

Abstract

Alopecia areata (AA) is an immune mediated, non-cicatricial, hair loss. AA may occur at any age and has an estimated lifetime incidence of 1.7%. Hair loss may range from localized, discrete patches or comprise the total body surface. The etiology of AA is multifactorial and thought to be caused by autoimmune, environmental, and genetic factors. Upon histological analysis, hair follicles afflicted by AA may reveal dense inflammatory cell infiltrate surrounding the bulbar region of anagen hair follicles. Dermatoscopic evaluation may reveal short, broken hairs with narrow proximal ends and thicker distal portions referred to as "exclamation mark" hairs. AA may be diagnosed clinically by the presence of often sharply demarcated round or oval-shaped areas of sudden, patchy hair loss. The rate of remission of AA is thought to be dependent on the amount of scalp involvement upon initial diagnosis. The general treatment approach to AA should include education regarding prognosis to facilitate informed decisions regarding treatment preferences. Patients should be directed to resources including opportunities to participate in clinical trials, products available to conceal hair loss, and psychosocial support upon initial diagnosis. Intralesional corticosteroids are considered to be first-line therapy for individuals experiencing limited disease and as adjunctive therapy in patients experiencing extensive disease. In patients with limited disease, topical corticosteroids have also shown clinical benefit particularly due to local anti-inflammatory effects. Topically applied agents may be used alone or in combination with additional treatment modalities and may be preferred over injections in the pediatric population. Minoxidil, methotrexate, or

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topical immunotherapy may also be considered based upon patient specific factors. A wide range of new therapeutic modalities with promising initial results are currently under investigation for the treatment of AA including statins, phosphodiesterase-4 inhibitors, Janus kinase (JAK) inhibitors, and platelet rich plasma (PRP).

Keywords
Alopecia areata · non-cicatricial · autoimmune · exclamation mark hairs · corticosteroids

A 22-year-old male presented with several focal patches of non-scarring alopecia on the scalp. He reported that the hair loss started after he had a cold on the right side of his scalp and gradually, more areas began to come up. He buzzed his hair short a few days ago so that we could evaluate his scalp more thoroughly. The patient denied hair loss elsewhere but reported he had a history of atopic dermatitis.

On physical examination, multiple well-demarcated patches of nonscarring alopecia were appreciated. Some patches had short, pointed hairs that were present (Fig. 3.1). Eyelashes and eyebrows appeared intact. He had a few dry, pink, scaly patches in the antecubital fossa bilaterally and on the trunk. Fingernail examination was within normal limits.

Based on the clinical case description, what is the most likely diagnosis?

1. Alopecia areata
2. Anagen effluvium

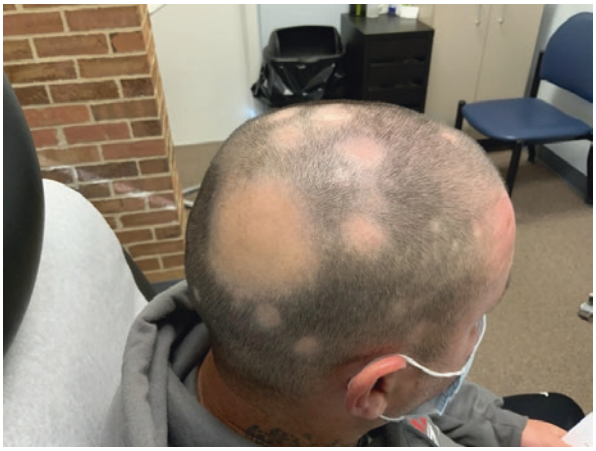

Fig. 3.1 Multiple discrete, well-demarcated patches of non-scarring hair loss

3. Androgenetic alopecia
4. Telogen effluvium

Diagnosis

Alopecia areata.

Discussion

Alopecia areata (AA) is characterized by non-scarring (also known as non-cicatricial) hair loss in localized areas. Non-scarring alopecia refers to hair loss that is due to alteration in the hair growth cycle, hair follicle size, hair breakage, or a combination of these with preservation of the hair follicle [1]. It is known that AA targets the hair follicle matrix but the condition itself has an unpredictable course with widespread phenotypic and genotypic variability. AA can be organized into three broadly distinct categories: (1) patch-type AA, characterized by round patches on the head or body; (2) alopecia totalis, defined as a near complete absence of hair on the scalp; and (3) alopecia universalis, which is described as complete hair loss on the body, face, and scalp [2]. The estimated lifetime incidence of AA is 1.7% [3]. AA can occur at any age, however, the typical age of onset is less than 25 years [4].

The etiology of AA is not entirely recognized but it is thought to be attributed to autoimmune, genetic, and environmental factors [4]. A loss of immune privilege of the hair follicle is thought to be a significant driver of the pathogenesis of AA [1]. Initiation of follicular damage is caused predominantly by CD8+ lymphocytes. CD4+ lymphocytes, natural killer cells, macrophages, Langerhans cells, and cytokines also contribute to the pathogenesis of AA, but to a lesser degree [5]. The hair follicle matrix epithelium undergoing early cortical differentiation has emerged as the primary target of cellular immune attack [1]. Localized degenerative changes within the matrix epithelium create weakness within the hair shaft and ultimately lead to breakage once the shaft emerges to the skin surface [1]. The primary histopathological feature of AA is dense inflammatory cell infiltrate surrounding the bulbar region of anagen hair follicles [1]. Dermoscopic examination of this phenomenon may reveal characteristic, although not pathognomonic, “exclamation mark” hairs, which are short, broken hairs where the proximal end of the hair is narrower than the distal portion. Additional dermoscopic features may include black dots, yellow dots, broken hairs, or short vellus hair [6]. However, preservation of the hair follicle and sparing of follicular stem cells results in the lack of ostensible scarring of the skin [7].

AA is typically diagnosed by its clinical manifestations including the presence of often sharply demarcated round or oval-shaped areas of sudden, patchy hair loss postulated to be caused by a premature transition from the anagen to the telogen phase within the hair growth cycle [8]. Hair loss may also present more diffusely and has the capacity to affect any hair-bearing region of the body. The Alopecia

Areata Assessment Tool (ALTO), a self-administered questionnaire designed to capture the hallmark features of AA and its three main phenotypes, aids clinicians in establishing a diagnosis of AA while discriminating AA from other forms of non-scarring alopecia such as androgenic alopecia, telogen effluvium and tinea capitis [9]. AA is also associated with other auto-immune mediated dermatologic diseases such as vitiligo, atopic dermatitis, psoriasis, and lichen planus.

Treatment

Patients with extensive AA, defined as >50% of the scalp, may experience lower remission rates as compared to those with limited scalp involvement, defined as <25%. Limited scalp involvement portends a better prognosis with remission rates up to 68% [10]. Counseling patients regarding disease prognosis may contribute to improved informed decisions regarding treatment preferences. Upon diagnosis, patients can use the National Alopecia Areata Foundation website (www.naaf.org) for resources including opportunities to participate in clinical trials, products available to conceal hair loss, and psychosocial support.

Intralesional corticosteroids are considered the first-line therapy for individuals experiencing limited disease and as adjunctive therapy in patients experiencing extensive disease [11]. Pilot studies have demonstrated a similar benefit of 2.5 mg/mL triamcinolone acetonide when compared to 5 or 10 mg/mL in patients experiencing patchy AA [12]. The triamcinolone acetonide dose should not exceed 20 mg per monthly session [12]. Adverse reactions to this form of therapy include skin atrophy at the site of injection. If patients fail to respond within 3–6 months, or skin atrophy is noted, therapy should be discontinued [13].

In patients with limited disease, topical corticosteroids have also shown clinical benefit particularly due to local anti-inflammatory effects. Topically applied agents may be used alone or in combination with additional treatment modalities and may be preferred over injections in the pediatric population [11]. Higher potency topical steroids may be used in adult patients, whereas less potent topical agents may be considered in pediatric patients. Side effects may include skin atrophy, acneiform eruptions, striae, telangiectasia, and skin discomfort associated with mild itching or burning [14]. In severe cases of diffuse AA, a brief course of oral corticosteroids could be considered to stimulate hair regrowth and modulate immunologic factors that contribute to AA prognosis [15]. However, relapse upon discontinuation is highly likely. Adverse reactions associated with systemic therapy which impede long-term use include hypothalamic-pituitary-adrenal axis suppression, worsening glycemic control, hypertension, and decreased bone density [11].

Topical minoxidil may assist in the maintenance of hair growth stimulated by other agents and may be used as adjunctive therapy [16]. Concentrations of topical minoxidil at 5% have been shown to be effective [17]. Adverse reactions of topical minoxidil include tachycardia, sparse vellus hairs, and scalp irritation including itching and dermatitis [18]. Notably, a recent clinical trial demonstrated that once-per-day dosing of oral minoxidil (OM) was found to be an effective and

well-tolerated treatment alternative for healthy patients encountering compliance barriers with topical formulations [19]. While not without a side-effect profile, this recent review found that OM at lower doses (<5 mg) was tolerable, with few and mild adverse effects [19]. By far, the most common adverse effect of OM was hypertrichosis, which was reported as mild and easily manageable. Other less common adverse effects include postural hypotension, dizziness, lower limb edema, and mild blood pressure changes [19].

Methotrexate as monotherapy or in conjunction with prednisone has been shown to stimulate successful hair regrowth in both pediatric and adult populations. Due to the adverse effects of methotrexate, such as abnormal liver function, gastrointestinal discomfort, and less commonly, lymphopenia and risk for pulmonary tuberculosis, methotrexate should be primarily considered in patients who have failed other standard therapies or who are suffering from severe AA [11, 20].

In adult and pediatric patients >10 years of age with extensive AA (scalp involvement >50%), evidence supports the implementation of contact sensitization. Contact sensitization involves the use of topical immunomodulators to induce localized allergic contact dermatitis and antigenic competition. Although the exact mechanism of action has yet to be elucidated, it is thought that topical immunotherapy results in the shifting of the target of T-cells from hair follicles to the epidermis through antigenic competition. An additional postulation involves an increase in T-regulatory lymphocytes through cytokine alteration resulting in a reduction of follicular inflammation [21]. Currently prescribed topical immunotherapeutic agents include squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP) [22]. A study demonstrated that DPCP yielded an overall response rate of up to 72.2% with efficacy further augmented by the concomitant use of anthralin [23, 24]. While efficacy has been demonstrated, DPCP possesses a high degree of relapse, resulting in the need for thorough patient education. SADBE therapy may be considered for patients refractory to DPCP therapy [11]. Topical immunotherapy with both SADBE and DPCP is contraindicated in pregnancy. Adverse reactions include localized lymphadenopathy and severe eczema [23].

Although further clinical trials and investigation are warranted, the pleiotropic effects of statin therapy were explored amongst patients with AA. In a small prospective pilot study, the administration of simvastatin at a moderate-intensity dose (40 mg) in combination with ezetimibe (10 mg) displayed hair regrowth in 14 out of 19 patients as early as 16 weeks of therapy [25, 26]. Additionally, the oral phosphodiesterase-4 inhibitor, apremilast, has shown promising results in mouse models and is currently under investigation in an ongoing clinical trial [27].

The use of Janus kinase (JAK) inhibitors is currently being explored in patients with AA. Specific agents that have been investigated include baricitinib, ruxolitinib, and tofacitinib [11]. A retrospective investigation of tofacitinib in adolescents aged 12–17 demonstrated hair regrowth amongst 69% of a study population containing 13 patients [28]. An open-label trial investigating ruxolitinib suggested that the degree of response may be variable and possesses a positive correlation with high interferon and cytotoxic T-lymphocytes levels at baseline [29]. JAK inhibitors carry a potential risk for serious adverse reactions including malignancy, infection, and

viral reactivation. Thus, larger-scale investigations of these agents are warranted and are currently underway [11].

Platelet rich plasma (PRP) isolated from venous blood samples has recently been explored in patients with AA. Bioactive molecules and growth factors within PRP have a regenerative impact on tissue, which leads to the potential use of PRP in the promotion of hair regrowth in AA [30]. A recent review highlighted a positively influential effect of PRP if at least three intradermal scalp treatments were administered at 4 to 5 week intervals for a total treatment duration of 4 to 6 months [31]. Further research is warranted to define its benefit, as limited studies have been conducted amongst patients with AA.

Key Points

- Alopecia areata (AA) is characterized by non-scarring (also known as non-cicatricial) hair loss in localized areas coinciding with varying phenotypic and genotypic presentations.
- Intralesional corticosteroids are considered the first-line therapy for individuals experiencing limited disease and as adjunctive therapy in patients experiencing extensive disease.
- A wide range of new therapeutic modalities with promising initial results are currently under investigation for the treatment of AA including statins, phosphodiesterase-4 inhibitors, Janus kinase (JAK) inhibitors, and platelet rich plasma (PRP).

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10-Year-Old Female with an Irregularly Shaped Patch of Hair Loss

4

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Abstract

Trichotillomania is a type of alopecia with a psychiatric etiology. This condition is characterized by repeated hair pulling resulting in hair loss that typically presents as irregular, patchy areas with numerous broken hairs. Diagnosis of trichotillomania is clinical, but a biopsy can be used to aid in diagnosis. The pathophysiology of trichotillomania is not fully understood but appears to have a genetic component. The HOXB8 gene may play a role. In addition, the SAPAP3 gene, which codes for postsynaptic components of glutamatergic synapses, has been studied and shown to possibly contribute to hair-pulling behaviors. Trichotillomania may simultaneously present with trichophagia which may lead to the development of trichobezoars in severe cases. Other complications include secondary infection at the site of hair-pulling. Trichotillomania is often associated with multiple different psychiatric comorbidities such as concurrent or past depression, anxiety, substance use disorder, and obsessive-compulsive disorder. Treatment of trichotillomania addresses the underlying psychological triggers of hair-pulling behaviors. Management varies based on the patient's age. In preschool age children, trichotillomania is likely to self-resolve with time. In school-aged children, behavioral therapy is more effective than pharmacologic therapy. First-line behavioral therapy consists of habit reversal training and stimulus control techniques. In adolescents and adults, combination therapy utilizing pharmacotherapy, psychotherapy, and management of comorbid psychiatric disorders suggests the highest clinical efficacy. First-line pharmacotherapy for trichotillomania is fluoxetine or clomipramine. Second-generation antipsychotics have

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moderate evidence of benefit in the management of trichotillomania. N-acetylcysteine and dronabinol are newer therapies being studied in the treatment of trichotillomania and evidence points toward potential clinical benefit. Other emerging treatment options such as the antioxidant milk thistle, probiotics, and inositol demonstrate a possible future direction of trichotillomania management; however, evidence of clinical benefit is significantly limited.

Keywords

Trichotillomania · Hair-pulling disorder · Psychocutaneous disorders Psychodermatology · Alopecia · SAPAP3

A 10-year-old female presented with one patch of non-scarring alopecia on the right parietal scalp. The patient said that it was present for about a month. Of note, the patient has a history of anxiety, which was diagnosed after her parent's divorce. The patient denied hair loss elsewhere.

On physical examination, a geometric patch of decreased hair density with broken hairs of uneven length was noted on the right parietal scalp. A few vellus hairs were present. Eyelashes appeared sparse but eyebrows were intact. The nails were very short, and the cuticles were jagged and inflamed. A hair pull test was negative. A Wood's light examination was negative for fungus.

Based on the clinical case description, what is the most likely diagnosis?

1. Alopecia areata
2. Trichotillomania
3. Alopecia due to nutritional deficiency
4. Alopecia due to tinea capitis

Diagnosis

Trichotillomania.

Discussion

Trichotillomania is a non-inflammatory, non-scarring alopecia with an underlying psychiatric etiology [1]. This disorder is typically diagnosed in childhood, with the most common age of disease onset being 10 to 13 years old. In childhood, both sexes are affected equally; however, in adolescence and adulthood, there does appear to be a predominance of females affected over males [2]. Trichotillomania has a lifetime prevalence of 0.6–3.4% in females and 0.6–1.5% in males. However, due to the stigma surrounding this condition, it is likely underdiagnosed in the general population [3].

Trichotillomania is characterized by repeated self-inflicted hair pulling resulting in hair loss and a significant negative impact on psychosocial functioning. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, it is classified as an obsessive-compulsive spectrum disorder [4]. Hair loss typically presents as irregular, patchy areas with numerous broken hairs. Various body regions may be involved in the presentation, including eyelashes, eyebrows, pubic and chest hair. The most common site of alopecia is the scalp, characteristically described as having a "Friar Tuck" appearance or tonsure pattern [5] (Fig. 4.1). The most common dermoscopic finding is broken hairs of varying lengths, which is found in nearly 100% of patients with trichotillomania; however, this finding is not specific to trichotillomania. Other specific findings include trichoptilosis (split ends), branched hairs (hair shafts with obliquely detached pieces), V hairs, tulip hairs (diagonal fracture of a hair shaft), coiled hairs, flame hairs (wavy thin hair), and the Mace sign (uniform broken terminal hairs with a bulging distal end) [6] (Fig. 4.2). In addition, the hair pull is negative [5]. In cases where the patient does not report hair pulling behaviors and clinical diagnosis is challenging, a biopsy with histological examination can be performed. The most specific histological finding is normally growing hairs adjacent to empty hair follicles in a non-inflamed scalp with the

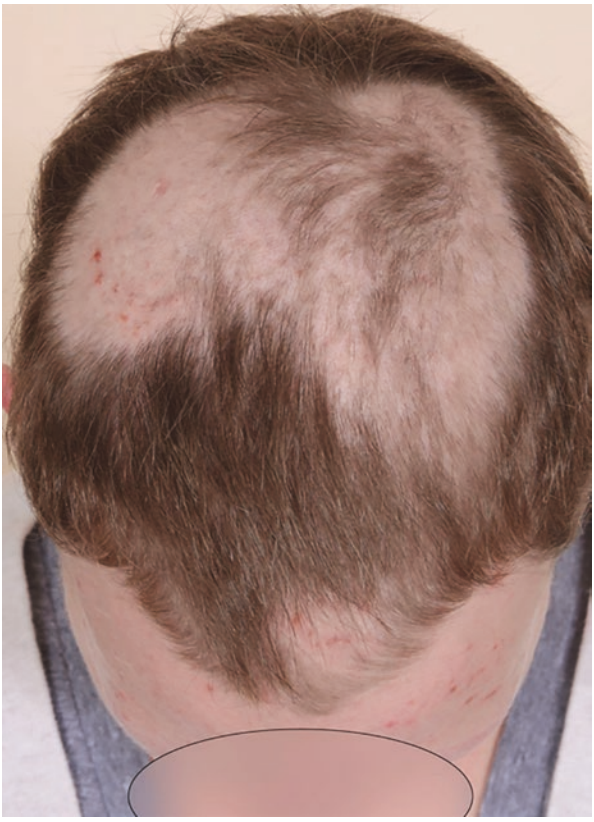

Fig. 4.1 Irregular and patchy areas of hair loss with a "Friar Tuck" pattern. Numerous broken hairs of varying lengths are present. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

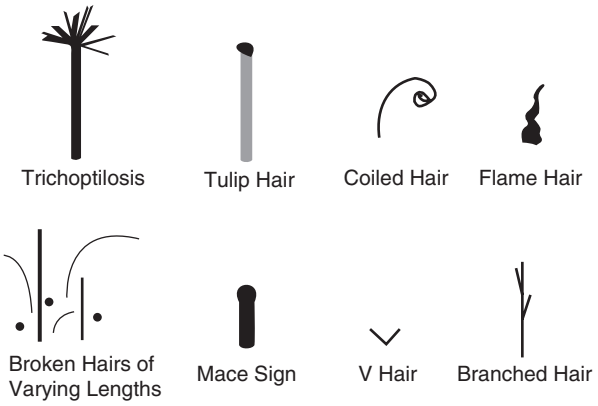

Fig. 4.2 Common trichoscopic findings in trichotillomania: Trichoptilosis: longitudinal splitting or fraying of the distal end of the hair. Tulip Hair: hypopigmented hair with pigmentation only at the tip. Coiled Hair: broken hair that is contracted and coiled inward. Flame Hair: semi-transparent wavey and cone-shaped hair. Broken Hairs: black dots illustrate the hair shaft remnant. Mace Sign: normally pigmented hair with a bulbous distal end. V-Hair: Two normal pigmented hairs that emerge from a single follicular ostium. Branched Hair: oblique detached pieces of the hair shaft

empty hair follicles commonly showing a transition to the catagen state. In addition, follicular plugging with keratin debris can also be appreciated [7].

The pathophysiology of trichotillomania is not yet fully understood. There appears to be a genetic component involved in disease development as HOXB8, SLITRK5, and SAPAP3 in knockout mouse models displayed excessive grooming habits similar to those seen in patients with trichotillomania [2]. The SAPAP3 gene codes for postsynaptic components of glutamatergic synapses. It is hypothesized that the SAPAP3 gene's role in disease pathophysiology has influenced the development of newer pharmacological therapies for the management of trichotillomania. SAPAP3 deletion in animal models is associated with over-grooming, anxiety-like behaviors, and cortico-striatal synaptic defects. The psychological etiology of trichotillomania is more widely understood. Hair pulling seems to be a coping mechanism used to subside negative emotions and stress with subsequent relief leading to repetition of the behavior. Other triggers of hair-pulling behavior include boredom, feelings of perfectionism, menarche, and pregnancy. Some evidence exists demonstrating cocaine use as a possible trigger as well [4].

Various complications and comorbidities may simultaneously present in patients with trichotillomania. Trichophagia, which is significantly less common in children, is observed in approximately 10–34% of adults with trichotillomania and may lead to the development of trichobezoars in severe cases. Trichobezoars are spherical collections of ingested hair within the gastrointestinal tract [2]. Patients presenting with trichophagia or trichotillomania with vomiting, pallor, or weight loss should be evaluated for trichobezoar formation [8]. Skin damage due to repetitive hair pulling and the possible use of trauma-inducing instruments to pull hair may lead to secondary infection [2]. Trichotillomania is often associated with multiple different

psychiatric comorbidities such as, concurrent, or past depression, anxiety, substance use disorder, and obsessive-compulsive disorder [9]. Significant feelings of shame and embarrassment are commonly present surrounding hair pulling behaviors, which often lead to social isolation, perpetuates continued hair pulling, and affects patients' willingness to seek diagnosis and treatment [9].

Treatment

Treatment of trichotillomania addresses the underlying psychological triggers of hair-pulling behaviors. Management consists of both pharmacologic and nonpharmacologic therapy and varies based on the patient's age. In pre-school age children, reassurance and parental education are the mainstays of treatment as trichotillomania is likely to self-resolve with time. Behavioral therapy has been shown to provide better outcomes in school-aged children compared to pharmacologic management. First-line behavioral therapy is habit reversal training, a form of cognitive behavioral therapy to develop a larger recognition of hair-pulling behavior and replace it with another sustainable behavior until the urge ceases. Habit reversal training is commonly paired with stimulus control techniques, where there are environmental modifications to make hair-pulling behaviors less favorable. This can include the removal of objects like mirrors or the addition of objects to distract from hair-pulling [10]. Other behavioral interventions include acceptance and commitment, metacognitive, exposure and ritual prevention, and dialectic behavioral therapies [10].

First-line pharmacotherapy for trichotillomania is selective serotonin reuptake inhibitors, namely fluoxetine, or clomipramine, a tricyclic antidepressant. Despite the common use of either drug in clinical practice, current literature demonstrates weak evidence of significant benefit in trichotillomania [11]. Second-generation antipsychotics such as olanzapine or risperidone have moderate evidence of benefit in the management of trichotillomania and may be a potential treatment option. Naltrexone has been studied in the pharmacologic management of trichotillomania due to its efficacy in addictive disorders; however, it shows very weak evidence of clinical benefit [10]. In adolescents and adults, combination therapy utilizing pharmacotherapy, psychotherapy, and management of comorbid psychiatric disorders suggest the highest clinical efficacy [10]. When adequate treatment and an interdisciplinary approach are sought and given, complete remission is usually achieved although, chronic functional impairment can be seen in treatment-resistant patients [4].

Recent advances in the treatment of trichotillomania utilize the hypothesized role of glutamate dysfunction in disease pathogenesis. N-acetylcysteine has been studied in the treatment of trichotillomania due to its regulation of glutamate toxicity in the brain. N-acetylcysteine is cost-effective and is well tolerated compared to mainstay pharmacologic therapies used in the management of trichotillomania [10]. This drug shows promising evidence pointing toward potential clinical benefit; however, there are conflicting studies suggesting N-acetylcysteine may not be effective in

children [2]. Dronabinol is another agent that has been studied as a potential treatment of trichotillomania due to a similar mechanism. This drug is a cannabinoid agonist that regulates glutamate cytotoxicity in the striatum. Further studies are needed to explore the possible benefit of dronabinol in trichotillomania management [10]. Other emerging treatment options such as the antioxidant milk thistle, probiotics, and inositol demonstrate a possible future direction of trichotillomania management; however, evidence of clinical benefit is significantly limited [10].

Key Points

- Trichotillomania is a self-induced alopecia characteristically presenting with irregular, patchy areas of hair loss most often located on the scalp although other body regions may be involved.
- Management of trichotillomania addresses underlying psychological triggers of hair pulling behavior and treatment approaches vary by age.
- First-line pharmacologic therapy is fluoxetine or clomipramine.
- Recent advances in the treatment of trichotillomania focus on addressing glutamate dysregulation that is hypothesized to be present in disease pathogenesis.

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28-Year-Old Female with Diffuse Thinning of the Scalp after Isotretinoin and Oral Contraceptives

5

Gabriel Mirhaidari, Richard Boyd, Suchita Sampath, and Shannon C. Trotter

Abstract

Drug-induced alopecia can be difficult to diagnose as determining a causative link between the introduction of a drug to the onset of hair loss requires both a detailed patient history as well as a clear understanding of hair growth cycling. Clinical history taking should include a comprehensive time frame dating back at least 3 months. The difficulty in diagnosis lies in detecting the specific offending agent. New case reports and studies are continually being published linking hair loss to a specific drug, however, these studies are routinely correlative in nature without a definitive biological linkage. Despite this, there are well-studied and reported classes of medications with strong evidence of causing alopecia that should be considered when there is high clinical suspicion of drug-induced alopecia. While drug-induced alopecia is often reversible upon cessation of the offending agent, this is often not an acceptable approach for life-saving and long-term use drugs such as chemotherapy agents, anticoagulants, and psychotropics. Furthermore, the emotional and psychological impact of hair loss without intervention poses serious risks to patient well-being and drug regimen compliance. For chemotherapy-induced alopecia, several targeted therapies exist with promising results such as scalp cooling. Topical and oral minoxidil may be used in those experiencing a drug-induced cause of telogen effluvium. More recent therapies focus on the use of growth factors such as VEGF and keratinocyte growth factor. Despite limited evidence-based therapies for the treatment of

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drug-induced alopecia, a high degree of interest remains in the field for continued investigations into new treatments.

Keywords

Drug-induced alopecia · Telogen effluvium · Anagen effluvium · Hair loss · Scalp cooling

A 28-year-old female presented with diffuse thinning of her hair on the scalp. She noticed that it started about 3–4 weeks after starting isotretinoin for her acne. At the same time she started taking isotretinoin, she also began an oral contraceptive pill to prevent pregnancy. She reported that it feels like her hair comes out in clumps at times. She denied hair loss elsewhere.

On physical examination, diffuse thinning of the scalp was noted with widening of the mid-line part (Figs. 5.1 and 5.2). A hair pull test was positive. A laboratory evaluation was negative for anemia, thyroid disease, or nutritional deficiency.

Based on the clinical case description, what is the most likely diagnosis?

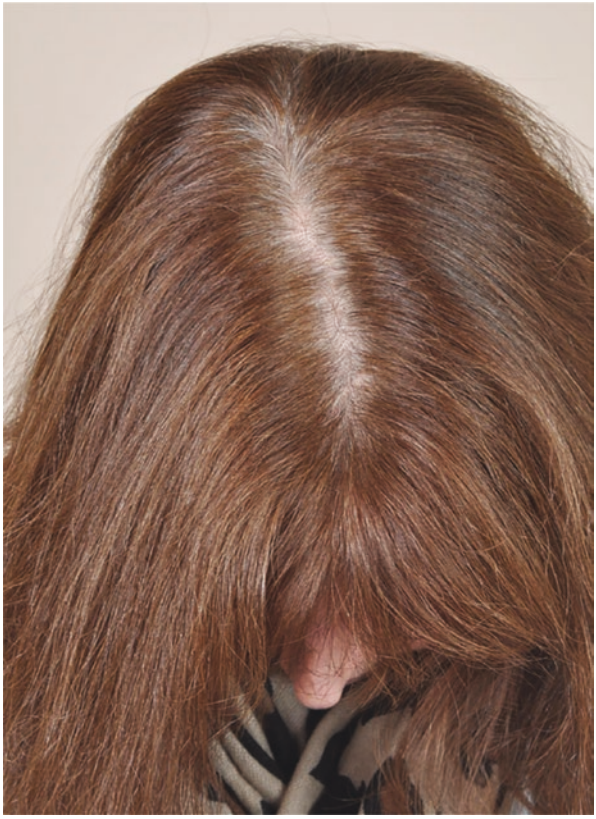

Fig. 5.1 Widening of the mid-line part. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

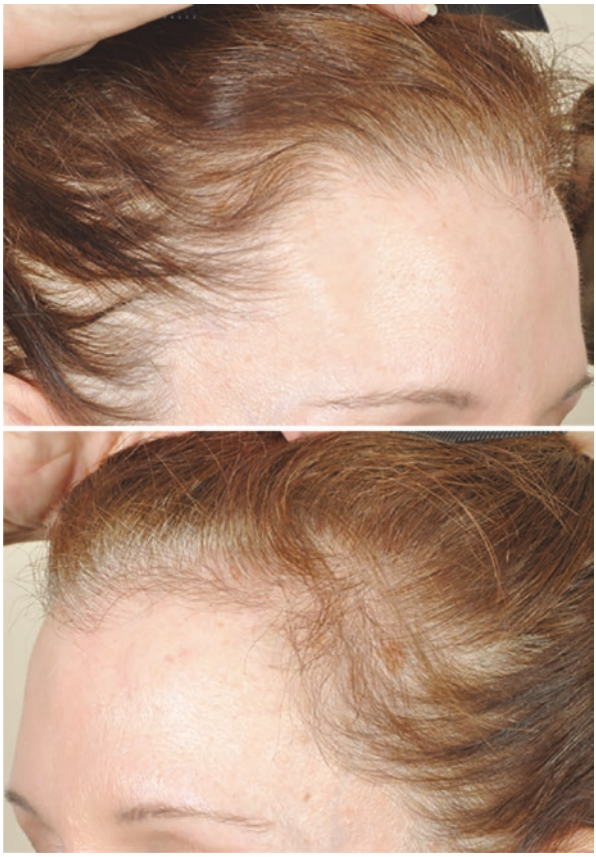

Fig. 5.2 Diffuse thinning along the frontal scalp. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

1. Alopecia areata
2. Androgenetic alopecia
3. Alopecia due to nutritional deficiency
4. Drug-induced alopecia (telogen effluvium)

Diagnosis

Drug-induced alopecia (telogen effluvium).

Discussion

Drug-induced alopecia can often represent a challenging clinical diagnosis. Determining a causative link between the introduction of a drug to the onset of hair loss requires both a detailed patient history as well as a clear understanding of hair

growth cycling. Briefly, hair growth is understood to consist of 3 phases: a growth (anagen) phase, a regression (catagen) phase, and a resting (telogen) phase [1]. The length of each phase and the percent of human scalp hairs in each cycle varies. Hairs can remain in anagen for up to 6 years with approximately 90% of scalp hairs being in the anagen phase at any given time [2, 3]. Thus, when considering a diagnosis of drug-induced alopecia, clinical history taking should include a comprehensive time frame dating back at least 3 months. Once an initial history and physical exam have ruled out other potential causes such as systemic autoimmune diseases and new environmental stressors, consideration can be made for linking medications to the onset of hair loss. However, even after diagnostic exclusion of other causes, identifying a single drug as the underlying cause can remain challenging. Part of this difficulty lies in the often unclear linkage of specific drugs in the literature to hair loss. New case reports and studies are being continually published linking hair loss to a specific drug, however, these studies are routinely correlative in nature without a definitive biological linkage. Despite this, there are well-studied and reported classes of medications with strong evidence of causing alopecia that should be considered when there is high clinical suspicion of drug-induced alopecia.

Drugs can induce hair loss through either anagen effluvium or telogen effluvium. Both processes present with distinct clinical characteristics and linkages to specific drug classes allowing narrowing of causative factors. Anagen effluvium presents with rapid (weeks) and significant (>80%) hair loss due to inhibition of cellular proliferation and will be discussed in a subsequent chapter. Unlike anagen effluvium, telogen effluvium presents insidiously (months after drug therapy initiation) [4, 5]. A range of drug classes have been linked to this presentation of alopecia including anticoagulants, psychotropics, antibiotics, retinoids, non-steroidal anti-inflammatory drugs, and beta-blockers. Evidence for drug-induced alopecia with anticoagulants such as warfarin, low molecular weight heparins, and new direct oral anticoagulants is reviewed in detail by Watras and colleagues [6]. Notably, there is significant uncertainty in the direct link between anticoagulants and hair loss given the limited number of case reports from the past 70 years. Part of this may be due in part to underreporting by clinicians and patients given the difficulty in linking anticoagulant use with the delayed onset of hair loss seen in telogen effluvium. Psychotropics have a more definitive linkage to telogen effluvium hair loss with lithium having a reported 12%–17% incidence of hair loss [7, 8]. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have additionally been described in the literature in limited case reports including fluoxetine, sertraline, trazodone, and imipramine [8–11]. Valproic acid induced hair loss has been reported to have an incidence ranging from 3.5%–28% with it notably being dose dependent [12, 13]. Reports of antibiotic induced alopecia remain rare/limited, possibly in part due to the often short duration of traditional antibiotic therapy. Of the available studies, antibiotics used to treat tuberculosis such as isoniazid are more frequently reported [14–16]. This may be in part due to the prolonged course required to effectively treat tuberculosis.

Treatment

While drug-induced alopecia is often reversible upon cessation of the offending agent, this is often not an acceptable approach for life-saving and long-term drugs such as chemotherapy agents, anticoagulants, and psychotropics. Furthermore, the emotional and psychological impact of hair loss without intervention poses serious risks to patient well-being and drug regimen compliance.

For chemotherapy-induced alopecia (CIA), several targeted therapies exist with promising results. Scalp cooling has been reported since the 1970s to induce vasoconstriction of the scalp reducing chemotherapy drug uptake by hair follicles as well as decreasing the biochemical activity of the follicles [17]. One of the earliest reports utilized a simple crushed ice in bags approach to cool the scalp with more recent devices from Paxman and Dignitana being commercially available for this indicated use [17–19]. A recent meta-analysis found scalp cooling to reduce the relative risk of CIA by ~33% indicating it as an effective treatment for preventing CIA in patients about to undergo or currently undergoing chemotherapy [20]. Topical application of 2% and 5% minoxidil, a readily available and affordable agent known to be effective in treating androgenic alopecia, has not shown similar success in treating CIA [21]. More detailed reviews do not recommend its use for treating CIA given the limited evidence of effectiveness [22, 23]. Interestingly, however, oral minoxidil has been shown to reduce hair loss in women with telogen effluvium, indicating a possible use for drug-induced causes of telogen effluvium [24].

Beyond these two classically described treatment modalities, more recent therapies have emerged with varying degrees of evidence. The use of a cocktail of growth factors such as VEGF, bFGF, and kGFG (QR 678 Neo) showed success in promoting hair growth in a limited number of patients with CIA [25]. Topical vitamin D3 analogues, thought to act directly on keratinocytes to promote differentiation, have been repeatedly investigated in the past 20 years for the treatment of CIA. Results have been inconclusive with no definitive evidence of its usefulness, but interest remains as illustrated by the recent completion of a phase I clinical trial [26–28]. Despite limited evidence-based therapies for the treatment of drug-induced alopecia, a high degree of interest remains in the field for continued investigations into new treatments. Approximately 15 clinical trials are currently registered under ClinicalTrials.gov investigating treatments such as platelet rich plasma, photobiomodulation, and keratinocyte growth factor [ClinicalTrials.gov respective identifiers: NCT04459650;NCT04036994;NCT04554732].

Key Points

- Drug-induced alopecia is largely a clinical diagnosis of exclusion based on a detailed patient history dating back at least 3 months.
- Classifying hair loss as drug-induced through either anagen effluvium or telogen effluvium based on the patient presentation can narrow suspicion for the potential offending drug class.

- Chemotherapy agents, anticoagulants, psychotropics, and select antibiotics have shown the greatest linkage to drug-induced alopecia in the literature.
- For clinical situations where drug cessation is not an option, or preventative hair loss prior to drug initiation is desired, scalp cooling therapy has shown the greatest clinical promise.

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55-Year-Old Female with Alopecia of the Scalp and Body After Chemotherapy

6

Michael Lawless, Sean Kirk, Suchita Sampath, and Shannon C. Trotter

Abstract

Anagen effluvium is diffuse hair loss that occurs after toxic or inflammatory insult to hair follicles during the anagen, or growth phase, of the hair cycle, disrupting bulb matrix epithelial cell mitotic activity. Most hairs (80%–90%) on the scalp at any given moment are in the anagen phase and thus, patients can experience a uniform loss of hair of this magnitude. The most common cause of anagen effluvium is classically seen in those undergoing chemotherapy, as dividing cells display high metabolic activity and thus take up the drug more rapidly, but other medications and inflammatory disorders have also been implicated. Hair loss in anagen effluvium is often reversible as the quiescent stem cells responsible for the initiation of follicular regrowth are unharmed. Removal of the offending agent or treatment of the implicated conditions often results in resolution and regrowth. The clinical picture with a thorough history and physical exam is key for diagnosis but clinicians may also rely on laboratory techniques such as microscopy and even biopsy for an anagen-to-telogen ratio. Management is centered around patient education, coping strategies, and decreasing the duration and amount of hair loss experienced. Patient education should focus on the natural course and likely reversibility of hair loss as well as daily preventative measures including grooming strategies and hair care. While these aid in the management of both psychological and emotional distress these patients may experience, it is important to assure social support and to offer counseling appropriately. With appropriate use, external devices, such as scalp cooling, which induces vasoconstriction, and scalp tourniquet application, which clamps arteries

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supplying the scalp, have been shown to reduce the degree of hair loss. Medical intervention, with agents such as minoxidil, which induces arterial vasodilation, may be used topically to promote hair growth but does not prevent hair loss.

Keywords

Anagen effluvium · Non-cicatricial · Alopecia · Chemotherapy · Scalp cooling · Minoxidil

A 55-year-old female presented with almost complete loss of hair on the scalp and the rest of the body, including her eyebrows and eyelashes. The hair loss started about 3–4 weeks ago after she started paclitaxel and carboplatin combination therapy for breast cancer. She reported that she anticipated the hair loss would occur but wanted to know if it is permanent or temporary.

On physical examination, the scalp is completely bald except for a few sparse hairs (Figs. 6.1 and 6.2). The eyelashes are sparse, and the eyebrows are thin. No hair is present on the arms. There were transverse grooves along her fingernails.

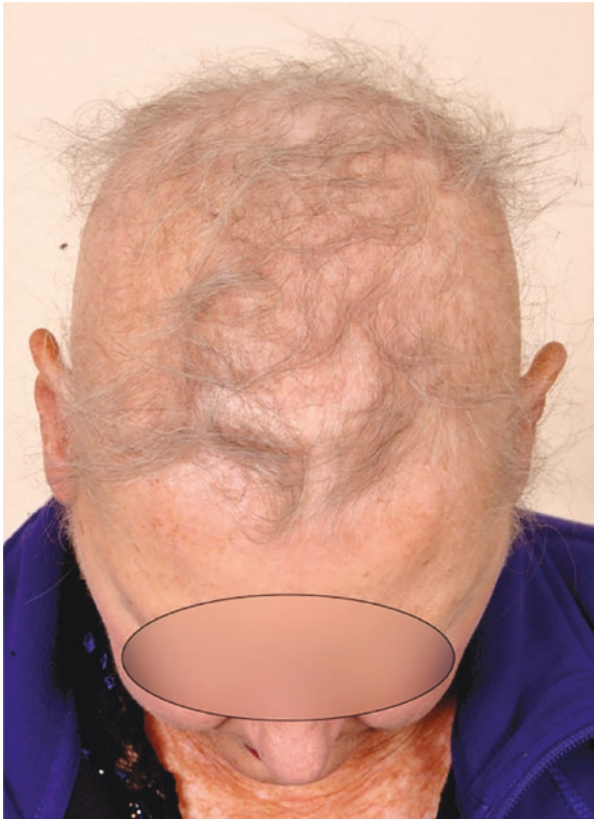

Fig. 6.1 Diffuse hair loss with only a few sparse hairs present after initiating chemotherapy. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

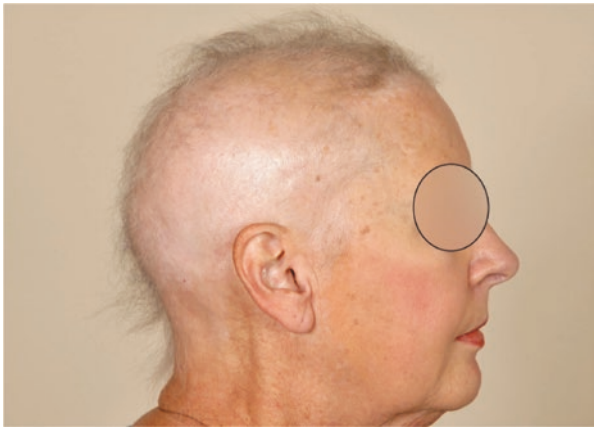

Fig. 6.2 Diffuse hair loss with only a few sparse hairs present after initiating chemotherapy. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

Based on the clinical case description, what is the most likely diagnosis?

1. Alopecia mucinosa.
2. Drug-induced alopecia (anagen effluvium).
3. Androgenetic alopecia.
4. Drug-induced alopecia (telogen effluvium).

Diagnosis

Drug-induced alopecia, anagen effluvium.

Discussion

Anagen effluvium (AE) is a form of non-cicatricial alopecia in which the affected anagen hairs are temporarily lost due to toxic or inflammatory insult [1, 2]. The toxic insults most commonly occur from medications, especially chemotherapy, but it also occurs with other inflammatory insults. As a result, AE has become synonymous with chemotherapy-induced alopecia (CIA) as other causes are rare and often not considered unless indicated by the clinical picture. AE in the context of drug-administration can be classified within drug-induced alopecia. Drug-administration and inflammatory conditions may also cause patients significant distress, so, in these scenarios, it is important to differentiate AE from telogen effluvium (TE) [1].

The inflammatory or toxic insult in AE results in diffuse hair loss as 90% of hairs on a scalp are in the anagen phase. The anagen phase, or growth phase, of the hair cycle lasts between 2 and 6 years during which epithelial proliferation of the bulb matrix cells forms the hair shaft. Consequently, these cells demonstrate both high metabolic activity and pigmentation which leaves them particularly susceptible to insult [1]. This insult disrupts epithelial proliferation, and impedes cellular mitosis

at the bulb matrix, damaging the shaft, and ultimately resulting in hair breakage or loss [1, 2]. This results in rapid, diffuse hair loss, often greater than 100 hairs per day over a period of 2–4 weeks [3]. However, since the quiescent stem cells that continue to initiate follicle growth are spared, hair loss is usually completely reversible [1].

AE is most commonly seen in patients receiving cytotoxic therapy. Shedding occurs in approximately 65% of patients using these therapies [4, 5]. Patients may begin to experience shedding within 14 days of administration of the offending agent and complete hair loss within 1 or 2 months of continued exposure [1, 5]. Most common medication culprits include chemotherapy agents which inhibit cellular proliferation of anagen hairs, causing apoptosis of the proximal bulb region [6]. Anti-microtubules, topoisomerase inhibitors, alkylating agents, and antimetabolites have been associated with alopecia with an occurrence of 80%, 60%–100%, greater than 60%, and 10%–50% respectively [2, 4]. Other less commonly implicated agents include isoniazid, levodopa, colchicine, cyclosporine, tamoxifen, allopurinol, bromocriptine, high-dose albendazole, and radiation therapy [1, 5, 7, 8]. AE secondary to these therapies is typically a reversible process that occurs naturally 1–3 months after the removal of the offending agent; however, while CIA is thought to follow this same pattern, recent studies have linked certain classes of chemotherapy to irreversible alopecia or permanent chemotherapy-induced alopecia (PCIA) [9, 10]. One study reported an incidence of 42.3% of PCIA in patients 3 years after undergoing chemotherapy, with taxane-based agents being the most offending [6]. This has also been reported with patients undergoing radiation therapy [1].

Heavy metals, such as thallium and mercury, are able to disrupt hair shaft formation by binding the sulphydryl group of keratins in the hair. Other heavy metals reported to be associated with AE include boron, and arsenic [3]. Patients would demonstrate systemic symptoms associated with toxic levels of the varying heavy metals as well as elevated blood levels.

Associated medical conditions include autoimmune and inflammatory disorders and severe malnutrition [1, 5]. Lymphocytes seen in alopecia areata infiltrate the hair follicle which causes the rapid progression from anagen to catagen and telogen and then back to the anagen phase. This continuous cycle changes the follicle's morphology into a short, incompletely keratinized or pencil point hair that is sensitive to trauma and breakage [11]. With pemphigus vulgaris, the autoantibodies disrupt hair growth as desmosomal proteins are expressed in the follicle epithelium [12]. Recently, there have also been case reports of COVID-19 related anagen effluvium associated with an urticaria and maculopapular rash that was associated with the massive inflammatory insult related to the disease [13].

Diagnosis of AE is typically made through history and physical exam. On examination, areas of hair loss will show no signs of active inflammation or scarring such as erythema, scaling, or pigmentation seen in cicatricial alopecia, but will show diffuse hair loss [1]. Patients retaining 10%–20% of hair in a uniform distribution is highly specific for AE, especially in the context of association with one of the previously listed medications or medical conditions [4, 5]. Microscopy may be

helpful to differentiate between conditions, such as TE, which presents with clumping, non-uniform distribution of hair loss with the onset of a significant life stressor, such as chemotherapy induction or systemic disease [5]. Microscopically, anagen hairs have full pigmentation with roots covered with inner and outer root sheaths, whereas telogen hairs lack inner and outer root sheaths, as well as pigmentation of the proximal shaft [1]. AE hairs will characteristically demonstrate a narrowing, fractured shaft as well [8]. A biopsy is rarely required for diagnosis but would show a low (15%) anagen-to-telogen ratio, differentiating it from TE. Follicles would also show no signs of inflammation, dystrophy of the inner sheath, or traction, distinguishing AE from alopecia areata, androgenic alopecia, and traction alopecia [1].

Treatment

Treatment of anagen effluvium is multifaceted, including decreasing the total quantity of hair loss, decreasing the overall duration of hair loss, increasing patient coping ability, and educating patients on the treatment course. Prior to the development of more current, promising treatments, management largely focused on patient education and the use of aesthetic devices. Patients may still choose this form of management but with the emergence of scalp cooling devices and hair growth medications, these may be utilized less often [14]. Current research is largely aimed at eliminating hair loss completely but has largely been unremarkable. Recent clinical trials have shown methods that decrease but do not eliminate hair loss. Cessation of implicating medications and treatment or the resolution of implicating medical conditions has been the only method to lead to complete resolution of anagen effluvium. Reports show that regrowth is scarce and less likely to occur in patients receiving high doses of radiation therapy [15].

Patient education has been at the forefront of management for patients experiencing or may be experiencing it in the future as many patients experience emotional and psychological distress [1]. It is imperative to educate patients not only on the probability of hair loss, but also on the current recommendations, course, and reversibility of it [5]. Recommendations for hair care before and during treatment include avoiding physical and chemical trauma to the scalp and hair (bleach, color, perm, irons, rollers) [1, 4]. Other recommendations include scarcely washing hair and the use of a satin pillowcase. Patients should be educated on coping strategies such as keeping their hair shorter, as this helps it appear fuller, as well as considering the use of an aesthetic covering, such as a hairpiece, wig, or scarf [4]. These have the added benefit of scalp protection from sun and cold exposure [1, 4].

Currently, the mainstay of treatment for medication-induced AE has been to reduce the quantity of offending agent delivered to the scalp follicles. This can be done with the application of a scalp tourniquet, clamping arteries, or inducing scalp hypothermia, causing arteriolar vasoconstriction. These techniques are especially effective for chemotherapy agents that have short half-lives and are rapidly cleared [4].

Scalp cooling has been well-studied and is shown to be highly effective in significantly reducing this effect [5]. Influencing factors include the type and dose of medication, as well as the degree of scalp temperature reduction. Studies have shown beneficial outcomes with temperature reduction below 22 degrees Celsius [16]. Mechanically, scalp cooling would be beneficial to reduce the delivery of any systemic medication to the scalp, with most evidence shown through studies in breast-cancer patients on anthracycline therapy [17, 18]. Therefore, the lowest efficacious dose would likely have the lowest risk of inducing AE. Studies have also looked at specific cooling systems, such as the Paxman PCS-2 (PAX). This system is most efficacious at reducing the risk of AE when used with a cold cap (CC) during therapy [19]. With the emergence and efficacy of this intervention, there is an enormous potential to ease the psychological burden of this unpleasant side effect and improve patient quality of life as some patients report treatment hesitancy and decline it in fear of hair loss [5, 20]. Common adverse effects include a sensation of cold, scalp discomfort, and headaches [4, 19]. Scalp cooling is contraindicated in patients with hematological malignancies due to its mechanism [4].

Scalp tourniquet devices have been shown to be effective in preventing hair loss in some studies, but populations and techniques have not been uniform, needing to account for different techniques, type of chemotherapy regimen, and amount of external pressure applied (4). While generally tolerated, side effects include headache and varying degrees of nerve compression that can induce scalp anesthesia [4, 17]. Contraindications include any brain or scalp metastasis [1, 5].

Pharmacological intervention is largely employed to reduce the severity and duration of hair loss experienced by patients. Topical minoxidil has been shown to reduce the period of baldness by about 50 days but does not prevent alopecia [1, 2, 17]. While minoxidil does induce local vasodilation to the scalp arteries when applied topically, the leading mechanism for which this drug stimulates hair growth include the increased activity of enzymes, such as adenosine triphosphate (ATP) synthase or sulfotransferase, but this is not fully understood [21, 22]. It has a good safety profile and tolerability with scalp pruritus being the most common side effect [23]. Due to the mechanism of arterial vasodilation, its use is only recommended after the discontinuation of the implicating agent or condition [2].

Numerous agents, such as small molecules, biologicals, and medications have shown promise in preliminary studies but failed larger clinical trials. These include keratinocyte growth factor, and combinations of topical dexamethasone, calcitriol, and calcipotriol or calcineurin inhibitors, interleukin-1, and calcitriol [1].

Key Points

- Anagen effluvium is diffuse hair loss caused by toxic or inflammatory insult to hair follicles during the anagen phase of the hair cycle.
- Toxic insult from patients undergoing treatment with chemotherapeutic agents is the most common cause of anagen effluvium, but other medications and inflammatory conditions have been implicated.

- Patient management is centered around patient education and coping strategies, as well as decreasing the duration of hair loss through mechanical and pharmacological interventions.
- Minoxidil is the mainstay of pharmacological therapy while the application of scalp cooling and tourniquets have shown benefit as external devices during chemotherapy treatment.

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47-Year-Old Female with Alopecia on the Frontal and Temporal Scalp

7

Alexandria LaSalla, Brittany Snyder, Suchita Sampath, and Shannon C. Trotter

Abstract

Traction alopecia (TA) is a commonly encountered cause of hair loss that results from repetitive pulling forces on the hair root. TA may present in both adults and children. Hair styling behavior that induces traction results in mechanical damage to the hair follicle and dermal papilla. The initial presentation of patients afflicted with TA involves hair loss in the areas subjected to increased tension with retained hair along the frontotemporal area. TA may be diagnosed clinically or upon histological analysis. When addressed at the early onset of disease, TA may be reversible. However, chronic TA as evidenced by scarring and fibrosis is typically irreversible. Early diagnosis and treatment are imperative, as treatment is dependent upon the stage of disease. The histological findings of early-stage TA may display hair follicle loosening with evidence of inflammation and folliculitis. Additional clinical findings may include trichomalacia and increased number of telogen and catagen hairs. Preventive education involving the avoidance of behaviors increasing tension on the hair should accompany pharmacotherapy. Educational interventions may include counseling on the avoidance of hairstyles causing pain as well as promoting hairstyles that will reduce traction. Patients should be counseled on avoiding brushing, chemicals, or heat, as these practices can increase the risk of hair follicle damage. The goal of treatment in TA is to reduce inflammation and promote hair regrowth. The mainstay of

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treatment in the pediatric population is education and prevention. Adults in the early stages of TA may be treated with regimens including topical or injectable corticosteroids. Potential side effects include dyschromia and hypopigmentation. Topical minoxidil use may also be considered in the adult population. If pustules or folliculitis is evident, topical antibiotics such as topical or systemic antimicrobial therapy may be considered. Later stage TA management includes surgical options, hair transplantation, or camouflaging techniques. Investigational therapies include topical alpha-antagonist, platelet-rich plasma, and laser-assisted drug therapies.

Keywords

Traction alopecia · Fringe sign · Trichomalacia · Tension hairstyles

A 47-year-old female complained of hair loss along the frontal scalp line. She reported occasional itching in the area and admitted to wearing her hair in braids over the past 15 years. She denied hair loss in the eyebrows or eyelashes.

On physical examination, there was hair loss noted along the frontal and temporal scalp (Fig. 7.1). Eyelashes and eyebrows were intact. Fingernails were normal in appearance.

Based on the clinical case description, what is the most likely diagnosis?

1. Traction alopecia.
2. Frontal fibrosing alopecia.
3. Trichotillomania.
4. Central centrifugal cicatricial alopecia.

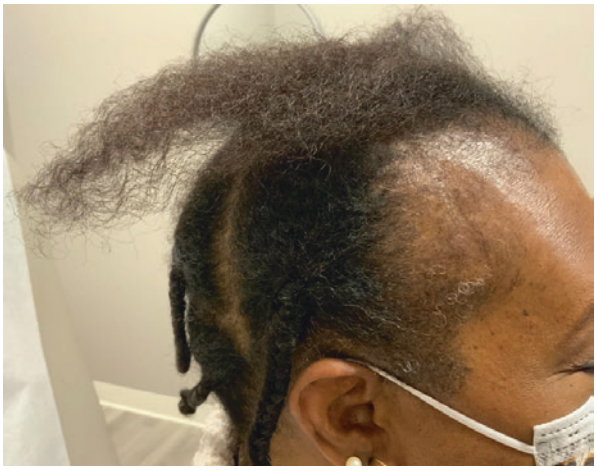

Fig. 7.1 Hair loss present along the frontal and temporal scalp

Diagnosis

Traction alopecia.

Discussion

TA is a common and preventable condition in children and adults where hair loss occurs due to repetitive pulling forces on the hair root. TA occurs in individuals with hair practices that induce strain on the hair for long periods of time. Higher prevalence has been reported in ballerinas and Sikh Indian males [1, 2]. However, TA affects one-third of women of African American descent due to cultural hairstyle practices that induce mechanical damage [3].

The consensus of recent literature determines that traction alopecia is caused by the hairstyle or practice rather than the hair type [4]. Hairstyles that can increase tension are ponytails, knots or buns, turban, braids, cornrows, extensions or weaves, twists, and dreadlocks. Hair practices such as chemical and thermal treatments can also increase the risk of TA [5]. Strain from pulling can mechanically damage the hair follicle and dermal papilla. The early form of TA, beginning in childhood or upon early identification in adulthood, can be reversible [5]. Clinically, patients with TA will present with patches of hair loss in the areas subjected to increased tension along with retained hair in the frontotemporal area of the scalp, known as the "fringe sign" [6]. Broken hairs and pustules may also be present and are the earliest clinical sign of TA [7]. The histopathology in the early stages shows hair follicle loosening with inflammation and folliculitis. Tension on the hair follicle can pull the root sheath to the surface represented by white hair casts on the hair shaft [8]. Other findings may include trichomalacia and an increased number of telogen and catagen hairs.

If tension-creating practices are not modified, a chronic form of TA develops resulting in scarring hair loss which may be irreversible [9]. An important identifier of late-stage TA is sclerosis and fibrosis. A common indication is the absence of hair with preserved follicular openings outlined in brown in the periphery of the affected patch on the scalp, corresponding to the pigmented basal cell layer of the follicular infundibulum that can be seen on histology [9]. The histopathology of later stages shows diminished hair density and areas with absent hair follicles or loss of follicular openings [7].

Treatment

Management of traction alopecia is dependent upon the stage at diagnosis. Chronic stages are refractory to treatment; therefore, diagnosis at early stages is imperative. Preventative education can help children and adults from developing TA and

should focus on avoidance of hairstyles causing pain as well as promoting hairstyles that will reduce traction such as looser braids and ponytails [10]. Patients should be counseled on avoiding brushing and refraining from chemicals or heat, as discontinuing these practices can decrease the risk of hair follicle damage [11]. However, hair practices can be of cultural importance and care should be taken when discussing with patients. The Skin of Color Society recommends a "Compliment, Discuss, and Suggest" culturally sensitive communication model for approaching TA [12].

Early diagnosis can be imperative to reversing and preventing chronic TA. Treatment is focused on anti-inflammatory measures and hair regrowth. Topical minoxidil 5% once or twice daily is used in the early stages of TA, however, it has shown variable effectiveness [13]. Combination treatment of steroids and minoxidil can maximize outcomes. Uwakwe et al. showed that combined use of topical minoxidil 5% and 3 intralesional triamcinolone acetonide injections 5 mg/mL at 6–8-week intervals showed halted progression of TA [6]. Topical corticosteroids may be used if there is evidence of inflammation. Akintilo et al. reports the use of topical fluocinolone oil 0.01% for tighter curl patterns or topical fluocinonide 0.05% solution for looser curl patterns once or twice a day until improvement occurs [10]. Oil-based solutions are preferred for curly hair to prevent breakage. Intralesional corticosteroids such as triamcinolone may be used when there is evidence of scaling, erythema, or tenderness [10]. Dosing has not been well documented in the literature, however Akintilo et al. reports using 2.5 or 5.0 mg/cc for 3 cc total to the affected hairline once a month [10]. A maximum dose should be limited to 20 mg per month to limit potential side effects of dyschromia and hypopigmentation. If pustules or folliculitis are evident, topical antibiotics such as topical clindamycin (1%) once daily can be used. For systemic treatment, oral antibiotics include the use of tetracyclines with an initial dose of 100 mg twice a day [14]. Reassessment should be done at each visit and consideration taken to decrease the dose to 20 mg twice a day after 3–4 months [10]. Primary management of TA in the pediatric population is hairstyle education and prevention. Minoxidil use for TA in the pediatric population has not been studied [15]. Consideration should be taken with steroid treatment in pediatric cases to prevent systemic side effects including growth delay.

Later stage TA management includes hair transplantation or camouflaging techniques. Surgical treatment should be considered if the patient has failed medical therapies. Hair transplantation techniques that have proven successful include punch grafting, micro-grafting and mini-grafting, and follicular unit transplantation [14]. Patients often undergo multiple sessions to achieve desired outcomes.

Further investigation into the treatment of TA have focused on α1-adrenergic receptor agonist therapy. The arrector pili muscle expresses the α1-adrenergic receptor and the contraction is hypothesized to increase the amount of force needed to pull the hair from the follicle [16]. Topical phenylephrine was used to induce piloerection and resulted in decreased hair loss in 80% of the subjects [16]. Other modes of therapeutic consideration include platelet rich plasma (PRP) and laser-assisted drug therapies.

Key Points

- Traction alopecia is mechanical damage to the hair follicle from hairstyles and hair practices that place tension on the follicular unit.
- Counseling and avoidance of specific hairstyles specifically in children are important first-line preventative measures for traction alopecia.
- Topical medications remain the current recommended clinical management for early reversible traction alopecia.
- Later stages of traction alopecia can be refractory to medical therapy but hair transplantation is a viable management option.
- Promising new therapeutic considerations include the use of topical α1- adrenergic receptor agonists to increase the amount of force needed to pull or damage the hair.

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36-Year-Old Female with Dry Skin and Thinning of the Eyebrows

8

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Abstract

Alopecia is a common physical finding in patients with hypothyroidism. Diffuse or partial non-scarring alopecia have been reported in up to 50% of patients with hypothyroidism. Cutaneous manifestations of hypothyroidism are theorized to be due to decreased thyroid hormone's role in peripheral cutaneous vasoconstriction, diminished sebum secretion, a slowed rate of hair growth, and an increased percentage of telogen hairs. Previous studies have shown normal telogen-anagen hair relationships were restored by returning the patient to euthyroid with standard thyroid hormone replacement. Alopecia in hypothyroidism is considered to be reversible, as long as the hair follicle is not atrophied from long-standing hypothyroidism. Autoimmune thyroid disorders may be more challenging to treat and require approaches beyond stabilizing thyroid hormone levels. In these cases, adjunctive hair loss treatments, such as topical minoxidil topical, laser caps/combs, scalp microneedling, corticosteroid injections, platelet-rich plasma injections, vitamin/mineral supplementation, and healthy diets are encouraged. One major challenge of treatment in any type of hair loss is patient compliance. Recent studies of oral minoxidil were found to be effective and a well-tolerated alternative for healthy patients having difficulties with topical minoxidil formulations. Newer treatments with platelet-rich plasma (PRP) injections are at the forefront of recent research and not only have shown to have effective outcomes in hair loss but also significantly improved the quality of life for patients.

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_8

However, further large-scale studies are needed to evaluate the efficacy of PRP as monotherapy and standardize treatment protocols.

Keywords

Hypothyroidism · Hypothyroid · Alopecia · Hair loss · Thyroid hormone · TSH · Minoxidil

A 36-year-old female reported thinning of the lateral portion of the eyebrows. She denied pulling at the eyebrow hair and said it had been gradual in nature. She also reported dry skin and her hair falling out, sometimes in clumps. She also noticed that her fingernails seem more brittle.

On physical examination, she had diffuse thinning of the scalp and a positive hair pull sign. Hertoghe's sign was present. Her fingernails had accentuated ridging and were short in length.

What screening test below is likely to diagnose the underlying condition most responsible for her hair loss and other clinical findings?

1. Ferritin
2. TSH
3. Complete blood count
4. Vitamin B12

Answer

TSH

Discussion

Hypothyroidism is a condition caused by an underactive thyroid gland resulting in a deficiency of thyroid hormones in the body. Hypothyroidism results from disruption anywhere in the hypothalamic-pituitary-thyroid axis and can be congenital, acquired, or iatrogenic. While iodine deficiency is the most common cause of hypothyroidism worldwide, in areas of iodine sufficiency, such as the US, autoimmune disease and iatrogenic causes are most common [1].

Hypothyroidism is a relatively common disorder with an estimated prevalence in the United States of 0.3% and subclinical hypothyroidism greater than 4%. The prevalence of hypothyroidism increases with age, and it is approximately 10 times more common in women than in men [2]. Among the many other clinical features, diffuse or partial alopecia, including the scalp, genital, and beard hair, has been reported in up to 50% of patients with hypothyroidism [3]. The alopecia experienced in these patients is categorized as non-scarring and reversible.

Thyroid hormones have many cellular effects. Nuclear thyroid hormone receptors are located near cellular DNA and initiate transcription, resulting in the formation of new proteins, which, in turn, affect the body's metabolic rate. In hypothyroidism, there is a reduced sensitivity of α- and β-adrenergic receptors to catecholamines causing a lower basal metabolic rate and reduced response to sympathetic stimulation. Decreased metabolic rate and central hypothermia cause peripheral cutaneous vasoconstriction resulting in characteristic cutaneous symptoms of hypothyroidism such as cold skin, xerosis, and pale skin [4].

Scalp and body hair are also affected by the reduction/loss of thyroid with hair texture becoming dry, coarse, brittle, and subject to an increased rate of loss. Thyroid hormone receptors (TRs) have been detected in epidermal keratinocytes, skin fibroblasts, hair arrector pili muscle cells, sebaceous gland cells, and several cell types that make up the hair follicle [5]. With low circulating levels of thyroid hormone and decreased stimulation of these thyroid hormone receptors on hair cells, the initiation and duration of hair growth are greatly decreased [5]. Hair findings are also thought to be, in part, due to diminished sebum secretion.

In addition to the slowed rate of hair growth, hypothyroid patients have an increased percentage of telogen hairs. In the scalp of a euthyroid person, approximately 90–95% of the hair follicles are in the anagen (active) phase and the remainder of hairs are in the telogen (resting) phase [6]. During the natural hair cycle, there is a physiological daily shedding of approximately 100–150 telogen hairs. If the older telogen hair is not pushed out by new hair re-entering the anagen phase, the shedding of telogen hair will produce visible alopecia. In comparison, a typical physiologic ratio of anagen/telogen hair would not result in noticeable changes.

Treatment

Studies have shown normal telogen-anagen hair relationships were restored with thyroid hormone replacement. Therefore, the current management is to treat the underlying hypothyroidism and return the patient to euthyroid [7]. In long-standing hypothyroidism, hair loss is likely irreversible due to atrophy of the hair follicles [8].

Guidelines for the treatment of hypothyroidism, drafted by the American Thyroid Association task force, concluded and advised that levothyroxine should remain the standard of care in treating patients with hypothyroidism. The task force did not find consistently strong evidence or superiority of alternative preparations (levothyroxine-liothyronine combination therapy, or thyroid extract therapy) over monotherapy with levothyroxine, in improving health outcomes for patients [9].

Thyroid replacement therapy should begin with a low dose of levothyroxine. In adults under 60 years old, levothyroxine starting doses of 50–100 μg daily can be used. While in older adults or patients with coronary artery disease, levothyroxine starting doses can be reduced to 12.5–25 μg daily. TSH levels should be monitored approximately 2 months after beginning treatment and/or with any change in dosage. Levothyroxine doses should be titrated based on the TSH levels, with the goal of treatment being a normal range TSH level. To increase treatment compliance, it

is important to educate patients that they may not experience full relief of symptoms until 3–6 months after normal TSH levels are restored [1].

One study found that the skin manifestations seen in autoimmune thyroid disorders may be more challenging to treat and require approaches beyond stabilizing hormone levels. In these cases, additional hair loss treatments may be encouraged. Additional, adjunctive treatments for hair loss may include minoxidil (topical), laser caps/combs, scalp microneedling, corticosteroid injections, platelet-rich plasma injections, vitamin/mineral supplementation, healthy diets, wigs, and concealers.

A complication of treatment in any type of hair loss is patient compliance which is multifactorial (length of treatment, cost, side effects, inconvenience). New research focuses on combating compliance by investigating treatment with oral minoxidil. Topical minoxidil solutions of 2% and 5% have been the mainstay treatment of hair loss but many patients struggle with the twice a day application, as well as the side effects of scalp irritation and change in hair texture. In a recent study, oral minoxidil doses between 0.25 mg and 1.25 mg were found to be effective and a well-tolerated alternative for healthy patients having difficulties with topical minoxidil formulations. The study ultimately concluded larger studies would be needed for standardized dosing treatment protocols [10].

A growing and recent amount of research on platelet rich plasma (PRP) injections have found effective outcomes in hair loss and may be an option for alopecia related to hypothyroidism. With the cost of the centrifuge system being reasonable, the injection being sourced from the patient's blood, the approximately 10-min procedure time, and little to no downtime for patients post-procedure, PRP injections for alopecia are attractive to both patients and dermatologists [11]. A recent study reviewed the findings of two high-quality randomized, placebo-controlled trials which both showed significant improvement of alopecia areata after PRP treatment when compared to placebo providing strong evidence of the efficacy of PRP [12]. Ultimately, although relatively safe, further large-scale studies are needed to evaluate the efficacy of PRP as monotherapy and standardize treatment protocols.

Key Points

- Alopecia is a common physical finding in patients with hypothyroidism due to decreased thyroid hormone's role in peripheral cutaneous vasoconstriction, diminished sebum secretion, and a slowed rate of hair growth.
- Treating the underlying hypothyroidism and returning the patient to euthyroid remains the mainstay management of alopecia in these patients.
- Additional use of adjunctive hair loss therapies such as minoxidil, vitamin/mineral supplementation, laser therapy, scalp microneedling, and healthy diets are encouraged in patients experiencing continued hair loss.
- Newer treatments such as platelet-rich plasma injections and oral minoxidil are being explored in clinical research/trials and show signs of efficacy and increased patient satisfaction.

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19-Year-Old Female with Hair Thinning and Heavy Periods

9

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Abstract

In cases of idiopathic alopecia, nutritional and laboratory-proven micronutrient deficiencies should be clinically suspected. Even with factors strongly associated with its onset, such as systemic conditions and emotional stress, a large majority of clinical cases of alopecia remain without a clear etiologic source. Nutrient deficiencies are often multifactorial and may arise due to genetic disorders, medical conditions, or comorbidities such as endocrine diseases (i.e. hypothyroidism), adverse effects of medications, or limited dietary practices. Micronutrient deficiency may represent a modifiable risk factor associated with the development, prevention, and treatment of alopecia. In addition, nutritional deficiencies may impact not only hair loss but promote unwanted structural changes and premature pigmentary alterations. While there is not a definitive first-line therapy for alopecia as a result of nutritional deficiency, studies indicate that diets rich in protein, vegetables, and soy promote hair growth and may be protective against androgenetic alopecia (AGA), alopecia areata (AA), and chronic telogen effluvium (TE). In addition, detecting low serum iron, vitamin D, or zinc levels could provide therapeutic insight, especially in high-risk groups. Although commonplace, the efficacy of biotin supplementation is widely debated. In a recent clinical comparative study evaluation amongst patients with TE, supplementation with combination oral nutritional components was shown to improve alopecia through both symptomatic resolution and stimulation of hair regrowth. Alopecia secondary to nutritional deficiency is rising as a differential clinical diagnosis as recognition of the vital roles micronutrients contribute in maintaining the

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_9

physical elements of hair growth and structural integrity steadily increases. Physicians can improve rates of diagnosis and therefore treatment of chronic alopecia by heightening awareness in regards to the interplay between a patient's medical history, active medications, and overall dietary lifestyle practices. Patients should also be counseled on the potential worsening of hair loss from excessive over-supplementation.

Keywords

Nutritional deficiency · Hair loss · Alopecia · Iron deficiency · Biotin

A 19-year-old female reported thinning of her hair over the past 2 years. She reported that her hair was so thick at one point she used to have it thinned out by her hairdresser. She denied having any family history of hair loss. She denied any history of emotional or physical stressors, such as illness, prior to her hair loss starting. She admitted to having a history of heavy periods. She brought photos of her hair from a few years ago to compare to what her scalp appears like today.

On physical examination, she had diffuse thinning of her hair as compared to the photos she brought in. Eyebrows and eyelashes were intact. A hair pull test was positive. There were no significant fingernail changes.

What nutritional screening test below is likely to diagnose the underlying condition most responsible for her hair loss?

1. Zinc
2. Selenium
3. Iron
4. 25-hydroxyvitamin D_3

Answer

Iron.

Discussion

The hair follicle is amongst the most highly metabolically active components in the human body [1]. The human scalp itself contains approximately 100,000 hair follicles that predominantly exist in the anagen, or growth phase, of the hair reproduction cycle, requiring a balanced combination of essential vitamins, minerals, and proteins to efficiently produce durable hair [1–3]. In addition to serving as physical elements of hair structural proteins, vitamins and minerals also function as physiologic cofactors necessary for metabolic and enzymatic reactions [4]. Micronutrients

are principal components of the hair follicle cycle. They serve as key agents in the process of cell turnover, a frequent occurrence in the hair follicle bulb where matrix cells rapidly divide [2, 5]. Vitamins and minerals are indispensable for proper cell growth and functioning; therefore, deficiencies in certain vitamins and or minerals may contribute to chronic hair loss, structural abnormalities, and premature pigmentary changes [2, 6].

Hair loss as a dermatologic condition is common, with close to 50% of men and women affected by pattern hair loss by the age of 50, coinciding with dramatic effects on quality of life [7]. Meta-analyses reveal that the role of nutrition and diet supplementation in treating non-scarring alopecia represents a growing area of inquiry [2]. Establishing the optimal balance of micronutrients creates hair follicle homeostasis, which is vital for healthy and actively growing hair.

Nutrient deficiencies are often multifactorial and may arise due to genetic disorders, medical conditions, or comorbidities such as endocrine diseases (i.e. hypothyroidism), adverse effects of medications, or restrictive dietary practices [1]. For example, those with vegetarian or vegan diets and menstruating females are commonly iron and Vitamin B12 deficient, potentiating increased rates of hair loss. A recent meta-analysis suggests diets that are rich in protein, vegetables, and soy promote hair growth and may be protective against androgenetic alopecia (AGA), alopecia areata (AA), and chronic telogen effluvium (TE). There may also be beneficial effects of anti-inflammatory diets, such as the Mediterranean diet or the gluten-free diet for those with celiac disease, as potential adjuvant therapies in alopecia disorders [8]. Although hair growth may be impacted by both protein malnutrition as well as micronutrient and other vitamin deficiencies, these associations are complex as indicated by an assortment of conflicting literature exploring the impact of micronutrients on common types of non-scarring alopecia such as AGA, AA, chronic TE, and female pattern hair loss (FPHL) [4, 6].

Treatment

Micronutrient deficiency may represent a modifiable risk factor associated with the development, prevention, and treatment of alopecia [2]. AGA and TE are two common types of hair loss in which studies indicate that supplementing the diet with both iron and vitamin D can improve symptoms [2]. A recent clinical comparative analysis compared the efficacy of two combination oral nutritional supplements as monotherapy for TE with one study group received a supplement composed of zinc, biotin, iron, vitamins A, C, E, and B complex, folic acid, magnesium, and amino acids of keratin and collagen and a second group received calcium pantothenate cystine, thiamine nitrate, medicinal yeast, keratin, and aminobenzoic acid. After 180 days, parameters relating to hair loss, hair volume, density of hair (scalp cover), hair shine, and hair strength were evaluated both clinically and via trichoscopy [9, 10]. At the initial 90 day evaluation, the first group showed significant clinical improvement for all parameters, while the second did not show any significant improvement in hair shine and hair strength. These significant clinical

improvements in hair loss, volume, and density signify that nutritional supplementation may be indicated in patients whose TE is related to dietary deficiencies.

In addition, studies have demonstrated a correlation between AA, a disease caused by an autoimmune attack on the hair follicle, and low vitamin D levels, suggesting that supplementation of vitamin D in the context of AA may provide symptomatic resolution [2]. Further investigative studies are required to determine whether any benefit exists for nutrition supplementation in the absence of a true documented deficiency. Importantly, certain supplementation may impose a risk of worsening hair loss as well as harness the potential for vitamin and mineral toxicities. For example, over-supplementation of selenium, vitamin A, and vitamin E have been linked to amplified rates of hair loss [6, 11, 12].

While laboratory-proven vitamin or micronutrient deficiencies should be corrected, the ideal range of micronutrient levels to either prevent or correct hair loss has yet to be elucidated [1]. For example, the association between iron deficiency and hair loss is a widely debated topic. However, studies have indicated that patients under 40 years of age with AA, TE, and FPHL displayed a significantly lower serum ferritin concentration as compared to healthy controls without hair loss [7, 8, 13]. A comparative retrospective analysis assessing iron and hair loss demonstrated that low serum ferritin levels were a contributing factor in worsening FPHL, further indicating that initial screening of iron status could provide therapeutic benefit [7]. Among those with TE who received oral iron supplementation, a dramatic decrease in the rate of hair loss was seen [7, 11]. Taken together, this data suggests that screening for serum iron levels is an appropriate initial work-up for the diagnosis and treatment of alopecia, especially amongst groups who are more susceptible.

Additionally, appropriate vitamin C intake is vital for patients whose hair loss is secondary to iron deficiency due to synergistic absorptive effects [2]. Other researchers have revealed that alopecia is a well-established sign of zinc deficiency, with proper supplementation stimulating hair regrowth [2].

Biotin, also called vitamin B7, is often marketed as a dietary supplement for strengthening hair, skin, and nails, although scientific data supporting this outcome are weak. Moreover, it has been demonstrated that proliferation and differentiation of cultured human follicular keratinocytes are not directly influenced by biotin [14]. Biotin deficiency is understood to be rare due to its widespread availability in diverse food sources and its production by intestinal bacteria which results in levels that are higher than the body's daily requirements [14]. It is important to recognize that many marketed biotin supplements exceed the daily recommended requirements. Although there is no upper limit for biotin intake, it is well reported that high biotin intake can interfere with tests that use biotin–streptavidin technology creating both falsely negative or falsely positive results [15]. Biotin related interference has been described in various laboratory tests such as thyroid-stimulating hormone, free T3 and T4, troponin, and can even interfere with infectious disease serologies and drug concentrations [15]. Of significance, the United States Food and Drug Administration described a case of biotin interference causing a falsely low troponin test which led to a missed diagnosis of a heart attack and the patient's death [16].

However, true biotin deficiencies may arise from rare genetic or acquired inborn errors of metabolism and satisfy justifiable reasons for individualized supplementation although biotin deficiency can most typically be corrected through nutrition [14].

In summary, heterogeneous, and limited data exist regarding the effects of protein, iron, zinc, fatty acids, amino acids, selenium, folic acid (vitamin B9), niacin (vitamin B3), biotin (vitamin B7), vitamin A, vitamin B12, vitamin D, and vitamin E supplementation on improving hair growth in the absence of a validly identified deficiency [1]. Laboratory-proven deficiencies of the aforementioned vitamins and nutrients should be corrected in addition to a systematic consideration of the patient's medical history, medication list, and dietary practices. Patients should also be counseled on the potential worsening of hair loss from excessive over-supplementation. Further research and larger controlled trials are necessary to determine the effect of micronutrient and vitamin supplementation on hair growth in patients suffering from various types of non-scarring alopecia secondary to laboratory-proven deficiencies.

Key Points

- Vitamins and minerals are essential for proper cell growth and functioning, therefore, deficiencies in certain vitamins and or minerals due to various genetic, medical, or lifestyle reasons may contribute to chronic hair loss, structural abnormalities, and premature pigmentary changes.
- Micronutrient deficiency may represent a modifiable risk factor associated with the development, prevention, and treatment of non-scarring alopecia.
- Treatment approaches for nutritional supplementation in cases of non-scarring alopecia are not standardized and should be considered an individualized treatment paradigm.
- Data suggests screening for serum iron levels is an appropriate initial work-up for alopecia and appropriate vitamin C intake is vital for patients whose hair loss is secondary to iron deficiency due to synergistic absorptive effects.
- There is lacking evidence regarding biotin's potential benefit as a treatment for alopecia as true deficiencies are rare and are caused by genetic or acquired inborn errors of metabolism.

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66-Year-Old Female with Itchy Scalp and Hair Loss

10

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Abstract

Lichen planopilaris (LPP) is a type of cicatricial alopecia that results in permanent hair loss commonly occurring in Caucasian and Indian women. LPP is considered a subtype of lichen planus whose characteristic skin findings may or may not be observed in patients diagnosed with LPP. There are several subtypes of LPP including classic, frontal fibrosing, and Graham-Little-Piccardi-Lasseur, each of which targets different areas of the body. The classic type usually occurs on the vertex and parietal scalp while frontal fibrosing alopecia targets the frontotemporal scalp. Graham-Little-Piccardi-Lasseur subtype presents with a cicatricial spreading pattern. The pathogenesis of LPP is not well understood, though there are several proposed mechanisms. One possible mechanism involves the upregulation of cell-mediated immunity pathways which lead to the targeting of follicular antigens and thus the permanent hair loss that can occur. Other affected pathways include upregulation of JAK expression which also results in the upregulation of proinflammatory cytokines and thus the destruction of the hair follicles. Treatment involves halting the scarring hair loss process before it occurs. First-line treatments typically include topical and intralesional corticosteroids. Novel treatments, based primarily on case studies, which target some of the primary pathogenic pathways include pioglitazone and tofacitinib. Treatment expectations should be discussed with patients before initiation as regrowth of

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_10

previously destroyed hair follicles may not be possible. It is also important to consider the effect of LPP on patients' mental health as this may affect the treatment goals and plan.

Keywords

Lichen planopilaris · Cicatricial alopecia · Tofacitinib · Frontal fibrosing alopecia · PPARγ

A 66-year-old female reported itching in her scalp and occasional flaking for about a year. She also noticed hair loss, more concentrated in the frontal scalp over the past few years, but assumed it was age-related. She stated that she was not bothered by the hair loss but was more annoyed with the pruritus. She had not treated the itching before but stopped using sunscreen in the area because she thought she might be allergic.

On physical examination, she had a smooth patch of alopecia lacking follicular openings along the frontal scalp line. The amount of recession was evident due to the lack of photodamaged skin in the area of hair loss that was present on the forehead. On further inspection, there was perifollicular erythema and scale noted in the scalp. She had mild thinning of the lateral portion of the eyebrows. Eyelashes were intact (Fig. 10.1). No fingernail changes were present, and her oral mucosa was normal.

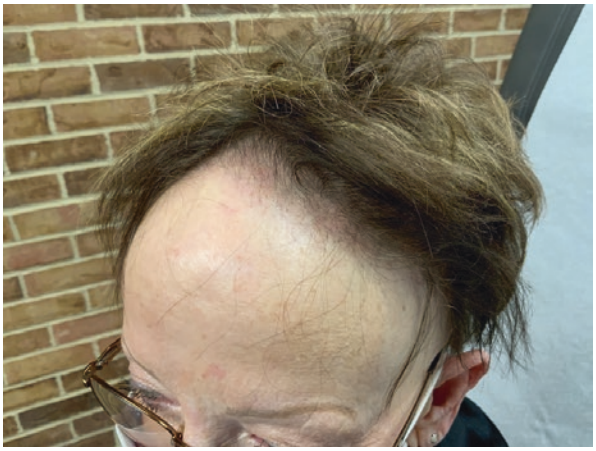

Fig. 10.1 Smooth patch of alopecia lacking follicular openings along the frontal scalp. Perifollicular erythema and scale are present on the scalp along with thinning of the lateral eyebrows. Note the demarcation of photodamage present on the forehead and not evident in the area of hair loss

Based on the clinical case description, what is the most likely diagnosis?

1. Folliculitis
2. Traction alopecia
3. Androgenetic alopecia
4. Lichen planopilaris, frontal fibrosing variant

Diagnosis

Lichen planopilaris, frontal fibrosing variant.

Discussion

Lichen planopilaris (LPP) is a chronic, primary, lymphocytic cicatricial alopecia that results in permanent, irreversible hair loss most commonly involving the vertex and parietal scalp [1]. Symptoms may include perifollicular erythema, pruritus, scaling, burning, and scalp tenderness [1, 2]. LPP is thought to be a follicular subtype of lichen planus where skin and mucous membrane manifestations may or may not be present in patients with this condition. Typically, this disorder affects middle-aged Caucasian and Indian women [1]. There is one classic type and two distinct clinical subtypes of LPP each with their own symptoms and characteristic patterns of hair loss. One subtype is frontal fibrosing alopecia which targets the frontotemporal hairline specifically in postmenopausal women. The other type is known as Graham-Little–Piccardi–Lasseur syndrome, which can present with cicatricial alopecia of the scalp, non-cicatricial hair loss in several different areas of the body, and keratotic follicular papules [2]. Other differentials for LPP include central centrifugal cicatricial alopecia, seborrheic dermatitis, discoid lupus, and pseudopelade of brocq. LPP can be diagnosed both clinically and histopathologically. Dermoscopy typically shows perifollicular scaling surrounding the proximal portion of the hair shaft [3]. Histologically, it is common to see subepidermal lymphocytic infiltrate, mucinous perifollicular fibroplasia, and wedge-shaped fibrosis that typically does not affect the deeper part of the follicle [3].

Classic symptoms of LPP can worsen when the skin is exposed to irritation, UV light, stress, and harsh chemical hair products which can result in triggering the pathways related to the overall pathogenesis of this disease [1]. Although not well understood, there are several proposed mechanisms for the pathogenesis of LPP, but the most widely accepted theory points to a possible autoimmune component [4]. Individuals with coexisting autoimmune conditions such as vitiligo and autoimmune thyroiditis have a higher likelihood of developing LPP. Cell-mediated immunity is thought to play a key role in the pathway to the development of LPP through

T cell mediated targeting of follicular antigens [1]. This results in inflammation and destruction of the hair follicle stem cells, which explains the previously described symptomatology and ultimately results in permanent scarring [3]. Other proposed pathways contributing to inflammation include upregulation of IFNγ which subsequently increases the number of activated cytotoxic CD8+ cells and thus an increase in JAK expression [5]. Furthermore, decreased expression of peroxisome proliferator-activated receptor (PPAR) γ has been shown to be related to LPP. When PPARγ expression is decreased, this results in lipid accumulation and can lead to the destruction of the pilosebaceous unit through the recruitment of proinflammatory cytokines [6]. In mice models, when the PPARγ transcription factor is deleted, mice can develop symptoms of LPP including scarring alopecia [6]. While the exact pathogenesis of this disease is not well known, treatment options utilizing these pathways have been developed and shown promise in patients with LPP.

Treatment

Since hair loss is usually permanent due to scarring, regrowth may not be possible. As a result, treatment is typically focused on decreasing disease progression, controlling symptoms, and stopping the scarring process before permanent hair loss occurs. First-line treatments typically include high potency topical corticosteroids, intralesional corticosteroids, and oral hydroxychloroquine [1, 3, 4]. First-line treatments may be used in combination with each other or with other second- or third-line treatments to achieve the best treatment outcome. These first line therapies are typically initiated when the disease is more localized and not widespread as they target and are applied to specific areas of the body. Second and third-line treatments include disease-modifying antirheumatic drugs such as methotrexate and mycophenolate mofetil [3, 4]. It is important to note that the efficacy of these treatments is based mainly on case reports making it difficult to find treatments that work for each patient. There are also side effects that should be considered when initiating these medications including their effect on the immune system. If the extent of the LPP disease is refractory to all other treatments, cyclosporine and oral steroids can be used; however, their relapse rates are high and also come with significant side effect profiles [3]. Since relapse is common and hair growth is not possible, it is also important to assess the psychological consequence that this disease may have on individuals. Stress can contribute to disease pathogenesis, so managing a patient's stress can have a significant impact on disease progression. Furthermore, managing patient expectations is key as stabilizing the disease may take at least 6 months and relapse can occur.

Several novel medications can be used if a patient is not experiencing improvement in symptoms and other first-line treatments have failed. Novel treatments used to treat LPP include pioglitazone and tofacitinib. Pioglitazone is typically used to treat diabetes because of its effect on PPARγ which can result in lower blood sugars. PPARγ has also been shown to play a role in the pathogenesis of LPP [3]. The absence, or downregulation, of PPARγ leads to the destruction of the pilosebaceous

unit [6]. Therefore, increasing or upregulating this pathway helps to decrease the infiltration of inflammatory cells and thus diminish the amount of scarring hair loss that is seen in this disease. Secondly, oral tofacitinib, a JAK inhibitor, has shown to be effective in treating alopecia disorders. When this pathway is inhibited, IFN gene expression is also inhibited which results in decreased activation of T cells and thus less scarring and inflammation [5]. In one study, using tofacitinib as a monotherapy or adjunctive therapy against LPP resulted in 80% of individuals involved in the study experiencing an improvement in symptoms [5]. It is also important to note the mild side effect profile that participants in this study experienced [5]. Furthermore, an early phase one clinical trial studying the safety and efficacy of ixekizumab, an IL-17A inhibitor, as a treatment for LP and LPP is currently underway [7].

Key Points

- Lichen planopilaris (LPP) is a chronic type of scarring alopecia that has an association with several other autoimmune conditions.
- The pathogenesis of LPP is not well understood, but autoimmunity and pathways that trigger inflammatory cytokine activation have been proposed.
- Treatment of LPP involves halting the scarring hair loss before it occurs, and patient expectations should be discussed prior to the initiation of treatment.

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50-Year-Old Female with a Burning Scalp and Hair Loss

11

Jennifer Viola, Michael Lawless, Suchita Sampath, and Shannon C. Trotter

Abstract

Central Centrifugal Cicatricial Alopecia (CCCA) is a primary, scarring, lymphocytic, alopecia that mostly occurs in middle-aged females of African descent. The hair loss pattern seen in CCCA usually begins at the vertex of the scalp and progresses in a symmetric centrifugal, or circular, pattern, resulting in irreversible scarring and loss of follicular pores. The pathogenesis is unknown but recent evidence suggests that it is a multifactorial condition influenced by genetics, grooming habits, and environmental factors which trigger an inflammatory response that ultimately leads to scarring. Diagnosis can be made through clinical presentation and characteristic dermatoscopic findings with possible use of biopsy. Laboratory values such as nutritional markers, CBC, and androgen levels can aid in ruling out other forms of alopecia. Typical dermatoscopic findings show peripilar white or gray halos, honeycomb patterns, perifollicular and/or interfollicular erythema, broken hairs, and pinpoint white dots. CCCA can be differentiated from LPP histologically but may also require the use of an elastin stain, which shows differences in fibrosis morphology. Patient management should include a progressive multifactorial approach focusing on early intervention with medications, patient education on additional preventative measures and disease course, as well as psychosocial support and counseling. Topical medical treatments include those that reduce scalp inflammation and provide symptomatic relief for patients, such as corticosteroids, tetracyclines, minocycline, calcineurin inhibitors, anti-seborrheic shampoos, and minoxidil. Treatment can progress to the concurrent administration of intralesional corticosteroid

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_11

injections, and oral immunomodulatory medications. Medications currently being explored for treatment include apremilast, gabapentin, clobetasol propionate, and JAK inhibitors. Invasive procedures, such as hair transplants, are considered last-line therapy. Additional techniques, including non-pharmacological methods such as camouflaging with hair pieces, wigs, and scalp micropigmentation have been beneficial for patients. These in conjunction with psychological support can be beneficial to patient satisfaction.

Keywords

Central centrifugal cicatricial alopecia · Alopecia · CCCA · Hair loss · Scarring alopecia · Lymphocytic alopecia

A 50-year-old female reported burning on her scalp and hair loss centrally that was present for about 18 months. She treated the area with tea tree oil with no improvement. She reported using a hot comb to style her hair in the past but stopped due to hair breakage. She also used extensions in the past but now wears her hair loose and does not have it braided.

On physical examination, there was a smooth, shiny patch of alopecia with few sparse hairs on the vertex of the scalp extending outward (Fig. 11.1). The eyelashes and eyebrows were intact. She had normal fingernails.

Based on the clinical case description, what is the most likely diagnosis?

1. Lichen planopilaris
2. Traction alopecia
3. Central centrifugal cicatricial alopecia
4. Lichen planopilaris, frontal fibrosing variant

Diagnosis

Central centrifugal cicatricial alopecia.

Discussion

Central centrifugal cicatricial alopecia (CCCA) is the most common scarring lymphocytic mediated alopecia that can cause permanent hair loss. It primarily affects young to middle-aged women of African descent with a varying prevalence between 3%–6% [1, 2]. However, there have been no population studies to date so the true prevalence may be unknown [3]. The etiology and pathogenesis are unknown but recent evidence suggests genetics, grooming habits, and environmental factors could trigger an inflammatory response [2, 4]. It is important to note that scarring, not inflammation, is a significant clinical observation [5]. Aggravating factors include heat, traction-inducing hairstyles, chemical relaxers, and texturizers [3].

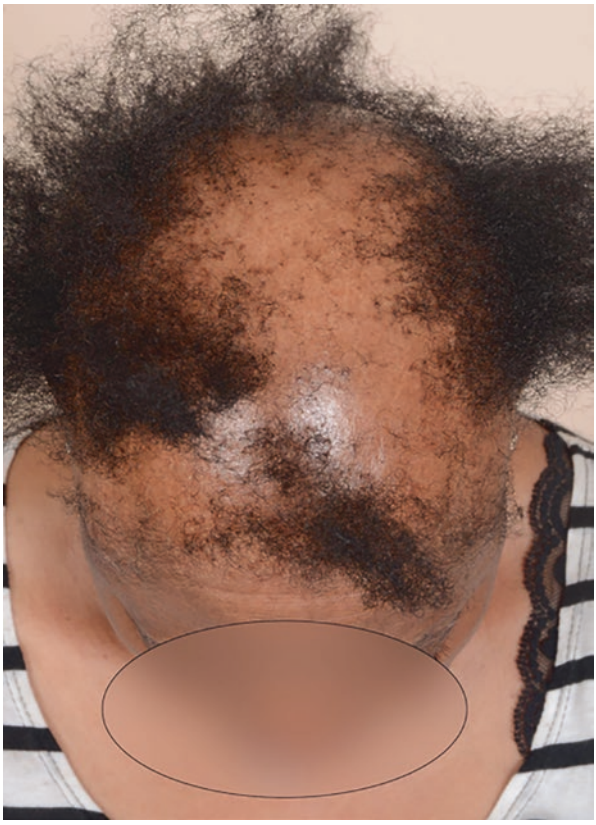

Fig. 11.1 Smooth, shiny, patch of scarring alopecia present on the vertex of the scalp extending centrifugally. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

However, the lack of statistically significant data as well as the presence of CCCA in women who do not practice the aforementioned hair routines, guided researchers to consider broader etiologies such as infection, autoimmune disease, and specific genetic factors [1].

Genetic factors may include familial inheritance. One pedigree study (n = 14 families) suggested CCCA can be inherited in an autosomal dominant pattern with partial penetrance [6]. A study concluded a variant of the PAD13 gene may be responsible for malformed hair shafts associated with CCCA [3, 7]. PADI3 is a peptide enzyme that post-translationally modifies other proteins that are essential for hair-shaft formation. Missense mutations that can occur within this gene affect highly conserved sequences, ultimately resulting in protein misfolding and decreased enzymatic activity [7].

Dysregulation of lipid metabolism may also play an important role in the disruption of hair follicle homeostasis. One gene expression study (n = 5) found a decreased expression of genes related to lipid metabolism and fatty acid synthesis in CCCA. The study also showed an increased expression of genes related to fibroblast regulation in CCCA. The increased expression is also present in uterine fibroid development and other fibroproliferative disorders, suggesting scar formation in CCCA occurs through a similar mechanism [5].

It is thought that disruption of balance or failure of communication between the epithelium regeneration and surrounding dermal papilla mesenchyme could result in hair loss [8]. This could occur secondarily to PPAR-γ downregulation disrupting lipid homeostasis and subsequent inflammation and fibrosis, as previously stated. However, more research is needed to explore the interaction of PPAR-γ and TGF-β in the wound healing pathway [8]. Once there is a better understanding of the pathogenesis, more targeted treatment options will follow [8].

The clinical presentation of CCCA is that of patterned progressive hair thinning. Thinning typically begins at the central vertex and spreads in a symmetric centrifugal pattern to the rest of the scalp [4, 5]. The subsequent scarring is irreversible and leads to the loss of follicular pores resulting in shiny affected areas [4, 5]. The periphery of these shiny affected areas can blend with surrounding, normal-appearing areas leading to no demarcation between affected areas and normal scalp. It is this periphery that is considered to be the most active for disease [1, 2]. Dermoscopic and histological analyses show that evidence of CCCA can be seen beyond the vertex scalp, extending into the normal-appearing tissue that lack clinically evident disease [9]. Presenting symptoms can range from asymptomatic hair thinning to burning, pruritus, scaling, erythema, tenderness, and follicular pustules on the crown.

Diagnosis can be made through clinical presentation and judgment but can also be aided by a biopsy [5]. Clinical judgment largely relies on negative findings for other disorders such as performing KOH prep and obtaining laboratory values such as nutritional markers, a complete blood count, and androgen levels [1]. Typical dermoscopic findings are peripilar white or gray halos, honeycomb patterns, perifollicular and/or interfollicular erythema, broken hairs, and pinpoint white dots [9]. Histologically, CCCA, like other primary scarring alopecia disorders, shows premature desquamation of the inner root sheath [1]. CCCA needs to be differentiated from lichen planopilaris (LPP), which presents with superficial perifollicular fibrosis, infundibular inflammation, and destruction that leads to free hair shafts in the dermis, similar to CCCA. However, it is differentiated by the presence of vacuolar lichenoid dermatitis with epidermal cytoid bodies and peri-infundibular hypergranulosis on histological evaluation [1]. CCCA may also present with a normal follicular pattern and preserved sebaceous glands. Clinicians may also consider using elastin stain to differentiate CCCA from LPP when the two appear identical on histopathology [10]. On elastin stain, CCCA will demonstrate tree trunk fibrosis, while LPP shows narrow wedge-shaped fibrosis [10]. This is used in conjunction with other clinical clues, such as the pattern of alopecia for diagnosis and treatment instead of relying solely on the pathology report.

Treatment

Treatment for CCCA should be multifactorial in its approach, with special attention paid to preventative measures such as topical medications, immunosuppressive therapies, psychosocial support, and patient education, including disease course and grooming education. There are invasive procedures that can be performed but these

are not considered first-line therapy. It is crucial to discuss prognosis and limited treatment options to manage patient expectations [1]. Since scarring causes permanent hair loss, management largely relies on prevention, with early intervention preferred, and patient education. Patients are advised to avoid relaxers and chemical treatments, heat, occlusive greasy moisturizers, and traction-inducing hairstyles like braiding [2]. It is important to screen family members for CCCA and encourage natural hairstyles for these patients [3]. These preventative recommendations are empiric at best and not substantiated by sufficient evidence.

No randomized controlled studies have addressed CCCA treatment. The main goal of treatment is to stabilize the condition to slow or halt hair loss. The least invasive treatment options include topical medications, such as corticosteroids, tetracyclines, minocycline, calcineurin inhibitors, anti-seborrheic shampoos, and minoxidil, to reduce inflammation and provide symptomatic relief [3, 4]. For disease not relieved with daily topical treatments, concurrent 5–10 mg intralesional corticosteroid injections at the leading edge can be performed at monthly intervals for 6–8 months [3, 4]. For active disease states, a short course of oral steroids may be considered. If improvement is seen after 2–6 months, a slow one-year taper of topical treatments can be discussed [1]. Persistently resistant disease may require administration of systemic medications like tetracyclines, hydroxychloroquine, antiandrogens, and immunosuppressives (mycophenolate mofetil and cyclosporine) for up to 1 year [3, 4]. Hair transplants can be considered in advanced, stable disease states where inflammation has been absent for 1 year. A test section should be performed first, due to concerns of graft survival on existing scar tissue. Additionally, non-pharmacological techniques such as camouflaging with hairpieces, wigs, scalp micropigmentation, and psychological support can be beneficial to patient satisfaction [3].

Due to the evolving understanding of the disease pathogenesis, new treatment considerations are being explored. Recently, JAK inhibitors have shown to be effective in treating alopecia areata. As a result, trials have begun to study their effectiveness for primary cicatricial alopecia patients [1]. An open label study concluded clobetasol propionate 0.05% emollient foam was a safe and effective treatment to decrease inflammation and provide symptomatic relief [11]. Currently, there are ongoing trials for therapies including apremilast, topical 6% gabapentin, gentle wounding to stimulate follicle growth, and biocellular regenerative treatment [12–16].

Key Points

- Central centrifugal cicatricial alopecia (CCCA) is a primary scarring lymphocytic alopecia that mostly occurs in middle-aged females of African descent and can cause permanent hair loss.
- CCCA usually presents as asymptomatic hair thinning that begins on the vertex scalp and progresses in a symmetric centrifugal pattern, resulting in irreversible scarring and loss of follicular pores.

- Pathogenesis is unknown but recent evidence suggests that multiple factors, such as genetics, grooming habits, and environment, could trigger an inflammatory response that ultimately leads to scarring.
- Treatment should be a progressive multifactorial approach focused on prevention through early intervention.

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40-Year-Old Female with Pink Scaly Patches in the Ears and on the Scalp

12

Bryce Demoret, Peter Noll, Suchita Sampath, and Shannon C. Trotter

Abstract

Lupus erythematosus is a multisystem disorder that predominantly affects the skin. Discoid lupus erythematosus is the most prevalent subset of chronic cutaneous lupus affecting, most commonly, women in their fourth and fifth decades of life. The lesions of DLE are characteristically well-defined, annular, erythematous patches and plaques and frequently present on photo-distributed areas of the skin. These lesions also tend to have secondary atrophy and scarring. As a result, when present on the scalp, DLE can progress to irreversible scarring alopecia. Although the pathogenesis is not entirely known, there is increasing evidence to suggest that ultraviolet light, environmental, genetic, and immunologic factors may contribute to the development of DLE. The early detection and treatment of DLE are essential to minimize the risk of scarring alopecia. Initial measures for individuals with DLE should involve education regarding exacerbating factors such as UV light exposure and tobacco use. Additionally, patients should be informed of the scarring nature of the disease process and that management aims to improve appearance, control acute lesions and limit further scarring. Treatment with topical and intralesional corticosteroids is considered first-line therapy. Novel treatment methods such as pulsed dye lasers and immune-modulating agents are being investigated for treatment-resistance DLE and have shown promise in initial clinical trials.

Keywords

Discoid lupus: Discoid lupus erythematosus · DLE · SLE · Alopecia · Cicatricial alopecia · Ultraviolet light · Autoimmune

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_12

A 40-year-old female complained of pink scaly patches on the inside of her ears and scalp. The scalp lesions were associated with hair loss and itched on occasion. She was prescribed hydrocortisone and terbinafine cream by her primary care physician with no improvement. Her health history was significant for migraine headaches.

On physical examination, there were pink scaly plaques noted on the left and right parietal scalp and the concha of the ears bilaterally. The lesions on the scalp lacked hair. A scalp biopsy was performed and showed a dense superficial and deep perivascular and periadnexal lymphocytic infiltrate, basement membrane thickening, follicular plugging, and mucin deposition in the dermis. The eyebrows and fingernails appeared normal.

Based on the clinical case description, what is the most likely diagnosis?

1. Lichen planopilaris
2. Traction alopecia
3. Discoid lupus erythematosus
4. Seborrheic dermatitis

Diagnosis

Discoid lupus erythematosus.

Discussion

Lupus erythematosus is a multisystem autoimmune condition that encompasses a variety of dermatologic manifestations. Discoid lupus erythematosus (DLE) is the most common form of cutaneous lupus erythematosus (CLE) and may or may not be associated with the development of systemic disease [1]. DLE generally follows a more benign disease course compared to other CLE subtypes. If the initial workup for DLE does not reveal any systemic manifestations of systemic lupus erythematosus (SLE), the chance of DLE progressing to SLE is less than 5% [2]. Roughly 60% of patients with DLE have scalp involvement, of which one third will suffer from scarring alopecia [3].

DLE occurs more frequently in women than men, has a higher prevalence in African American women than Caucasian women, and affects individuals in their fourth and fifth decades of life [4]. The lesions are frequently photodistributed and affect the head and neck areas. Due to the scalp being a sun-exposed area, the scalp is a common presentation for DLE [5]. The propensity for the scalp increases the risk for DLE-related scarring alopecia and subsequently can significantly affect patients' quality of life. DLE lesions often appear as well-demarcated, erythematous, scaly macules or papules that gradually develop into an indurated discoid plaque with an adjoined scale. These plaques can extend into the hair follicle, causing alopecia [1] (Fig. 12.1). The lesions are often associated with hyper- and

hypo-pigmented patches (Fig. 12.2). DLE lesions may last for many years and are associated with extensive scarring.

The pathogenesis of discoid lupus erythematosus is multifactorial. Research suggests genetic, environmental, ultraviolet light, medications, cigarette smoke, and possibly viral infections can contribute to disease prevalence and severity. Exposure to UV light (UVL) is a well-documented modifiable risk factor that increases the severity of DLE lesions. In particular, UVB and UVA2 wavelengths have been implicated in the formation of DLE skin lesions [2, 6]. After direct UV exposure, the transcription factor IRF5 significantly increases in the skin, potentially leading to the photosensitivity associated with DLE [7]. Several other immunologic factors contribute to the pathogenesis of DLE. These immunologic factors include abnormal antigens and autoantibodies, hypermethylation of MHC class I molecules, plasmacytoid dendritic cell (PDCs), and natural killer cell (NKs) cell proliferation, CD8 T-cell activation, Th1 cell abnormalities, and IgG and IgM deposition in normal skin tissue [2]. This vast immune response plays a prominent role in the primary cicatricial alopecia caused by DLE. Cytotoxic lymphocytes can destroy the stem cells of hair follicles and cause the scarring associated with DLE. The primary histopathologic features associated with DLE are erythema, telangiectasias, follicular plugging, and resolution with scar formation [2].

The lesions are characteristically well-defined, annular erythematous patches or plaques with follicular hyperkeratosis. Plaques that extend into the hair follicle give the lesions a characteristic "carpet tack sign" and frequently result in scarring alopecia and permanent hair loss [8]. Dermoscopy of the scalp in patients with DLE reveals white patches, branching capillaries, keratin plugs, and areas of reduced follicular ostia [9]. Blue-grey dots in a speckled pattern located within white patches of DLE may also be visualized upon dermoscopy [9]. Additionally, plasmacytoid dendritic cells containing the marker CD123 in clusters of 10 cells or more, favors a diagnosis of scarring-DLE alopecia [10].

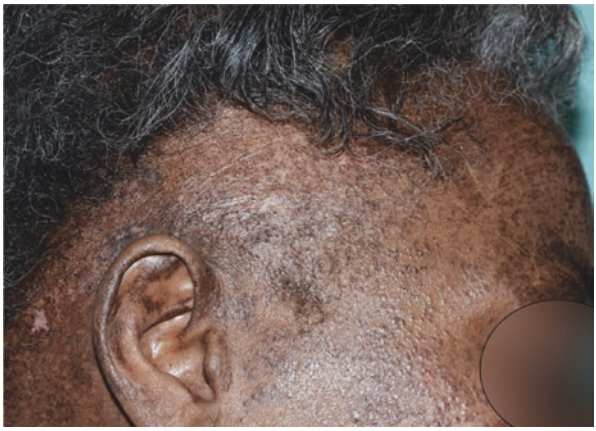

Fig. 12.1 Scaly patches with follicular plugging and scarring alopecia along the temporal and auricular scalp. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

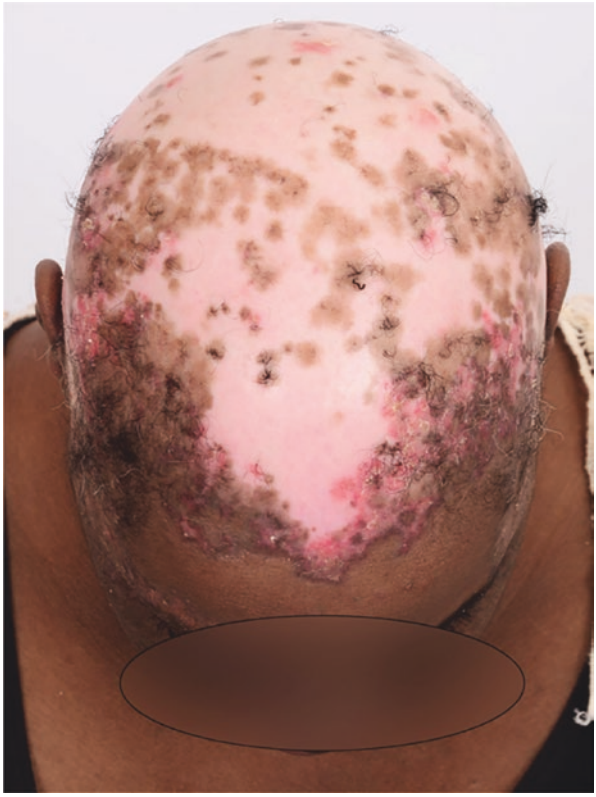

Fig. 12.2 Smooth, hypopigmented patches with scarring alopecia and a scaly, inflammatory anterior border. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

Treatment

The early detection and treatment of DLE are essential to minimize scarring and ultimately prevent permanent alopecia. General measures for individuals with DLE should involve non-pharmacologic methods such as eliminating exacerbating factors such as UVL [11]. Physical blockage of UVL with brimmed hats and the use of broad-spectrum sunscreens with an SPF of ≥30 are recommended [12]. Additional preventative measures include tobacco cessation, the avoidance of photosensitizing medications, and medications causing drug-induced lupus. When non-pharmacological management of DLE cannot be achieved, medications should be considered in the treatment plan. DLE management aims to improve the patient's appearance, control acute lesions, and limit scarring alopecia [13].

First-line therapy of acute DLE consists of topical corticosteroids, topical calcineurin inhibitors, and intralesional corticosteroid injections. Recent studies suggest that patients with DLE saw greater clinical improvement when treated with high-potency topical corticosteroids, such as fluticasone 0.05% cream, compared to medium- or low-potency topical corticosteroids (hydrocortisone 1.0% cream) after 6 weeks [14]. Although high-potency topical corticosteroid creams are preferred, patients must be educated about the possible side effects of prolonged usage

(cutaneous atrophy, telangiectasia, striae), especially when treating lesions on the face. If not resolved with topical corticosteroids, topical calcineurin inhibitors and intralesional corticosteroids should be considered.

Topical calcineurin inhibitors have specific advantages when treating facial lesions as they are not associated with cutaneous atrophy. Side effects of these medications include transient pruritus and burning, which typically resolve after one to two weeks [15]. The approved topical calcineurin inhibitors for DLE include tacrolimus 0.03% and 0.1% ointment and pimecrolimus 1.0% cream. Upon initiation, the treatment response with calcineurin inhibitors is usually seen between 4–8 weeks. Unlike corticosteroids, long-term therapy with calcineurin inhibitors is well tolerated and helpful in sustaining remission [15]. Unsuccessful treatment with calcineurin inhibitors or topical corticosteroids may warrant intralesional steroid injections with triamcinolone (3–5 mg/mL). If DLE does not respond to topical corticosteroids or calcineurin inhibitors, intralesional corticosteroid injections such as triamcinolone (3–5 mg/mL, multiple 0.1 mL, spaced 1 cm) are warranted.

Systemic therapy is considered second-line due to a greater risk of adverse events and is reserved for patients with DLE refractory to topical treatment regimens. The antimalarial hydroxychloroquine (200–400 mg/day) has historically been used in CLE management and is considered the first-line systemic agent for DLE [16]. A retrospective study of 200 patients with DLE demonstrated an adequate clinical response in 60% of patients within the first six months after long-term treatment with hydroxychloroquine [17]. Retinopathy is the most common adverse event associated with hydroxychloroquine and recommended guidelines for ophthalmologic examinations should be followed. For patients who do not respond to hydroxychloroquine therapy alone, quinacrine (100 mg/day) may be added in combination for additional benefit [18].

Other treatment modalities such as pulsed dye lasers, azathioprine, systemic retinoids, methotrexate, and thalidomide are documented in patients with refractory DLE [16]. However, these treatment options are generally considered third-line therapy. More recent clinical trials involving biological and immunological agents such as ruxolitinib, etanercept, and secukinumab are under investigation. One potential treatment option for treatment-resistant DLE is ASF-1096, which is primarily composed of R-salbutamol in an oil-in-water emulsion [19]. R-salbutamol has anti-inflammatory properties and hence could help treat glucocorticoid-resistant lesions. One study found that new and non-hypertrophic lesions responded well to treatment, but old hypertrophic lesions were difficult to treat [19]. The most common side effects associated with R-salbutamol included mild irritation to the applied area [19]. While this is a novel treatment option, it has shown promise in treating DLE-resistant lesions and warrants more extensive clinical trials.

Key Points

- Discoid lupus erythematosus (DLE) most commonly presents in isolation from systemic lupus and is more prevalent in middle-aged African American females.

- Early identification and management of discoid lupus erythematosus (DLE) can help prevent permanent scarring and related alopecia.
- Patient education should focus on avoiding exacerbating factors such as excessive sun exposure, tobacco smoking, and associated provoking medications.
- Medical management begins with topical and intralesional immunosuppressant therapy and more extensive or refractory cases may warrant systemic anti-inflammatory agents.
- Ongoing clinical trials with novel treatment regimens and promising biologics are currently under investigation to manage DLE scarring alopecia.

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60-Year-Old Male with Painful Patches of Hair Loss on the Scalp

13

Trent Walker, Catherine Grace Hobayan, Suchita Sampath, and Shannon C. Trotter

Abstract

Folliculitis decalvans (FD) is a rare, primary, neutrophilic, cicatricial alopecia that usually occurs in young to middle-aged adults. FD initially presents as a distinct follicular pustule or papule that may be tender, painful, or pruritic. This area begins to slowly expand creating irregularly shaped patches of scarring alopecia as the follicular orifice is lost. Active disease continues peripherally in an expanding pattern. FD has a waxing and waning course with periods of more intense disease presentation followed by periods of reduced activity. FD almost exclusively affects the scalp with preferential activity at the vertex and occiput. Another notable characteristic of FD is tufting of hair characterized by multiple hairs (5–20) emerging from the same dilated follicle. The first step in the diagnosis of FD involves gathering a general medical history and a bacterial infection history as *Staphylococcus aureus* is commonly cultured from the active lesions. Following this, a thorough examination of the scalp should be performed to look for follicular ostia, perifollicular erythema, or follicular hyperkeratosis. Treatment for FD has traditionally focused on controlling inflammation and the microbiota through the use of steroids and antibiotics. Destruction of hair follicles results in permanent hair loss; therefore, therapy is targeted at active lesions to prevent future permanent hair loss. Photodynamic therapy (PDT) with red light as well as immunotherapies are potential treatments usually in those patients who are refractory to steroids and antibiotics. Both of these treatment options

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_13

lack robust evidence and are associated with mixed outcomes. As FD can be a painful, distressing, disease that is scarring in nature, patient counseling is essential for comprehensive patient care.

Keywords

Folliculitis decalvans · Cicatricial alopecia · Hair tufting · Staphylococcus aureus · Photodynamic therapy

A 60-year-old male presented with tender, firm lesions on the central scalp of 6 months duration. He reported pustules throughout his scalp that he would pick at constantly. He was concerned because he now noticed hair loss within the patches and thickening of the skin. He denied hair loss elsewhere. He tried ketoconazole shampoo with no improvement.

On physical examination, there were irregular, atrophic patches of hair loss with surrounding pustules at the periphery that were tender to touch. Hair tufting was present. The eyebrows and eyelashes were of normal density. The fingernails were normal.

Based on the clinical case description, what is the most likely diagnosis?

1. Discoid lupus erythematosus
2. Dissecting cellulitis
3. Tinea capitis
4. Folliculitis decalvans

Diagnosis

Folliculitis decalvans.

Discussion

Folliculitis decalvans (FD) is a primary neutrophilic cicatricial alopecia [1]. Primary cicatricial alopecia is characterized by inflammatory destruction of the hair follicle, resulting in permanent hair loss, in contrast to secondary cicatricial alopecia, where non-follicular disease results in the follicle destruction (e.g., pemphigus vulgaris, burns) [2]. FD is considered a rare cause of alopecia, and in a large multicenter retrospective study was found to account for 3% of 3133 diagnoses of alopecia and 11% of 840 diagnoses of cicatricial alopecia [3]. FD presents in both men and women but shows male predominance. FD usually occurs in young to middle-aged adults and more frequently in African-American patients than in Caucasian patients [1, 4].

Clinically, FD initially presents as a distinct follicular pustule or papule that may be tender, painful, or pruritic (Figs. 13.1 and 13.2). Expansion ensues as adjacent papulopustules appear on the periphery of the erythematous lesion. Slowly, irregularly shaped patches of scarring alopecia occur, and the follicular orifice is lost. Active disease continues peripherally in an expanding pattern. Yellow-gray scales may be present, especially around the follicles, as well as follicular hyperkeratosis, erosions, and hemorrhagic crusts. FD has a waxing and waning course with periods of more intense disease presentation followed by periods of reduced activity [1]. FD may affect any area of the scalp but preferentially affects the vertex and occiput and often presents with multifocal lesions [2]. It almost exclusively involves the scalp, though there have been rare cases affecting the beard, face, and nape of the neck [5]. Another notable characteristic of FD is the tufting of hair characterized by multiple hairs (5–20) emerging from the same dilated follicle [2]. Despite its classification as a neutrophilic alopecia, FD may possibly be a continuum of disease with eventual lichenoid features depending on levels of bacterial biomarkers [6].

Histologically, FD commonly presents with an intrafollicular and perifollicular neutrophilic infiltrate. As the disease progresses, this infiltrate spreads into the surrounding adventitial dermis. Foreign body giant cells may be present and are localized to ectopic portions of the hair shaft [2]. In late stages of the disease, chronic inflammation results in the presence of more plasma cells and fewer neutrophils. These advanced lesions may also present with dermal fibrosis [2]. On dermoscopy,

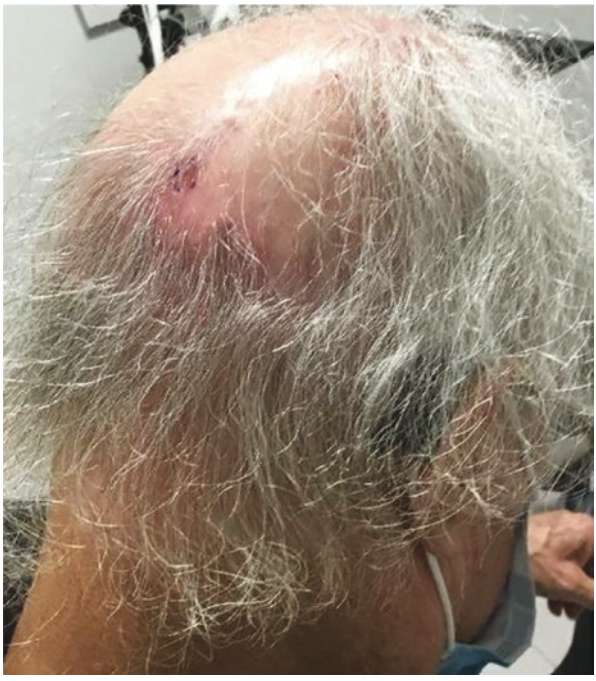

Fig. 13.1 Tender erythematous follicular pustule. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

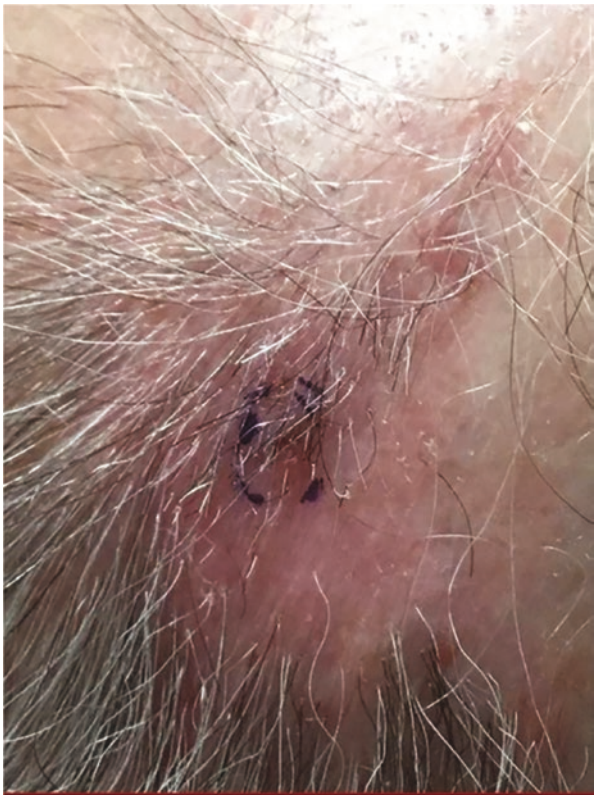

Fig. 13.2 Magnified image of the tender, erythematous follicular pustule that is the initial finding in FD. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

FD presents as fused follicular infundibula and thickened interfollicular keloid-like areas with tufted hairs [7].

While there are multiple theories on the etiology of FD, the pathophysiology is unknown. Many of the theories involve *Staphylococcus aureus* as it is commonly cultured from FD pustules. This finding has driven the use of antibiotics as the principal treatment for FD. However, it is important to note that while *S. aureus* is commonly cultured from active lesions, FD is not simply a bacterial infection. One study proposed that the epidermal barrier may be defective in FD. This study compared the superficial and subepidermal microbiota and found *S. aureus* colonized in 16 out of 20 patients in non-lesional, subepidermal skin in patients with lesions. As *S. aureus* was present in non-lesioned subepidermal skin, the implication is that FD could be due to a rupture of the epidermal barrier resulting in the invasion of opportunistic bacteria [8]. Other theories range from a congenital abnormality of follicular orifices to a deficiency in the host immune response to *S. aureus* autoimmune process [9]. The postulation that the host cell-mediated immunity is defective may explain the effectiveness of biological medications such as adalimumab in some refractory cases of FD [10]. More research is required before the etiology of FD can be determined conclusively.

The first step in the diagnosis of FD involves gathering a general medical history and a bacterial infection history. Following this, a thorough examination of the scalp should be performed to look for follicular ostia, perifollicular erythema, or follicular hyperkeratosis. Measurements, bacterial cultures, and biopsies of the active lesions should be taken to determine the diagnosis [9].

Treatment

Due to the erythematous pustules with abnormal bacterial findings, treatment for FD traditionally has focused on controlling inflammation and the microbiota through the use of steroids and antibiotics [10]. Treatment of FD is most effective for patients with active disease. Destruction of hair follicles results in permanent hair loss; therefore, therapy is targeted at active lesions to prevent future permanent hair loss. As FD can be a painful, distressing, disease that is scarring in nature, patient counseling is essential. Additionally, camouflaging techniques (e.g., wigs, caps, hairpieces, etc.) are possible solutions, but they can be a reservoir for *S. aureus*; therefore, cleansing with antiseptics and frequent switching between headpieces is important.

Current evidence of therapies is primarily based on observational studies or small sample sizes that lack external validity. One comparative case-control study was performed that focused on the impact of *S. aureus* on FD before and after an anti-staphylococcal treatment of rifampicin and clindamycin [8]. *S. aureus* was found initially in 0/20 of the control patients and 16/20 of the patients with FD. After treatment, 70% of patients had a decrease in pustule and crust formation and approximately 60% of patients had a decrease in the peripilar erythema. The *S. aureus* colonies almost completely disappeared, only remaining positive in two patients. Despite efficacious treatment, peripilar erythema persisted in about 80% of patients to a moderate degree [8].

For mild to moderate FD, topical antibiotics and topical and intralesional steroids are first-line therapies and can be used especially for those desiring to avoid the systemic side effects of antibiotics and steroids. The potency of the topical steroids is such that they can be applied locally 2 or 3 times per week in conjunction with topical antibiotics to treat FD of slight or moderate severity. Treatment with intralesional steroids is among the most effective methods for treating FD, and they can be used once every 3 months for slight inflammation in mild to moderate FD. Oral antibiotics, such as tetracyclines or azithromycin, may also be administered for mild to moderate FD [11, 12].

As FD becomes more severe, the above treatments may still be considered. However, for refractory cases, a combination of rifampicin with clindamycin is more effective with a longer duration of response. Clindamycin 300 mg twice daily with rifampin 300 mg twice daily are dosed for 12 weeks. Systemic corticosteroids may also be effective to control FD [11, 12]. Isotretinoin is beneficial for FD that is not well controlled with previous treatments, and other cases demonstrate that it can

result in complete remission of FD and may warrant further consideration as a primary treatment [12, 13].

Photodynamic therapy (PDT) with red light is another potential treatment, though it lacks robust evidence and is associated with mixed outcomes [14]. To date, the largest study of PDT in FD selected 13 patients with previously poor outcomes using various topical and oral agents and placed them on a course of PDT with no other therapy. All showed improvement during treatment, and at 12-month follow-up, nine patients maintained well-controlled symptoms while four relapsed [15]. Insufficient evidence supports using PDT as first-line therapy, but it may be beneficial to use in refractory cases of FD.

Lastly, there have been reports of various immunotherapies namely secukinumab, adalimumab, hydroxychloroquine, and infliximab successfully treating FD, and one case utilizing apremilast [11, 16, 17]. All of these patients were refractory to traditional treatments and responded favorably to their respective immunotherapy. This may indicate an underlying defect of the immune system in individuals with FD, especially in refractory cases. Additionally, the efficacy of platelet-rich plasma (PRP) was demonstrated in the treatment of two cases of refractory FD. Further research is needed to understand the successful symptomatic control achieved with PRP, but its antimicrobial and anti-inflammatory effects are promising for FD treatment [18].

Key Points

- Folliculitis decalvans (FD) is a rare cause of alopecia identified by active erythematous disease on the periphery of lesions.
- Despite bacteria in active pustules, a simple bacterial infection is not the sole cause of FD manifestation.
- Initial treatment is topical/oral antibiotics, like tetracyclines, and rifampicin/clindamycin and corticosteroids.
- Future therapies, especially in refractory cases, may involve PDT and various immunotherapies.

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44-Year-Old Male with Tender, Draining Lesions and Hair Loss on the Central and Posterior Scalp

14

Abigail Wissman, Morgan Amigo, Suchita Sampath, and Shannon C. Trotter

Abstract

Dissecting cellulitis of the scalp (DCS), a lesser known member of the follicular occlusion tetrad, is a rare but morbid condition characterized by draining sinuses and pustules leading to primary cicatricial alopecia. This condition primarily affects young African American men, aged 20–40 years. The cause of DCS is not well understood but it is thought to be partially caused by hyperkeratosis leading to follicular occlusion. The initial presentation of DCS is commonly one or more papules or pustules at the vertex of the scalp. When left untreated, these pustules develop into boggy nodules that form sinus tracts to other lesions. Patients often report flares of symptoms with itching, pain, and foul odor being common complaints. As the disease progresses, patients may notice hair loss at the side of nodules. Microscopy may be helpful in distinguishing DCS from other diseases of the scalp. The histopathology of DCS will vary with stage. In earlier stages, lesions demonstrate dense neutrophilic predominance with associated lymphocytic, histiocytic, and plasmacytic infiltrates. As the inflammation progresses to a more chronic state, lesions contain granulomas consisting of lymphocytes, plasma cells, and foreign-body giant cells. Treatment options also depend on the stage of the disease and range from antibiotics and scalp hygiene, steroids, isotretinoin, immune modulators, and in extreme cases, scalp resection. Patients

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_14

will require counseling on the psychosocial aspects as well as the relapsing and remitting nature of the disease.

Keywords

Dissecting cellulitis · Cicatricial alopecia · Follicular occlusion · Staphylococcus aureus · HLA-B27

A 44-year-old male presented with boggy, painful lesions on the central and posterior scalp. He complained that some of the areas would drain at times and that the hair stopped growing in those areas. He also reported low back and hip pain but assumed it was arthritis from working as a firefighter. Of note, his history was positive for acne as a teenager and a pilonidal cyst in his twenties that was treated surgically.

On physical examination, scarring alopecia was present on the central and posterior scalp with nodules that would drain with pressure (Fig. 14.1). Keloidal scarring was present. The eyebrows and eyelashes were of normal density. The fingernails were normal. Of significance, he was later referred to his primary care physician and diagnosed with sacroiliitis.

Based on the clinical case description, what is the most likely diagnosis?

1. Discoid lupus erythematosus
2. Dissecting cellulitis
3. Tinea capitis
4. Folliculitis decalvans

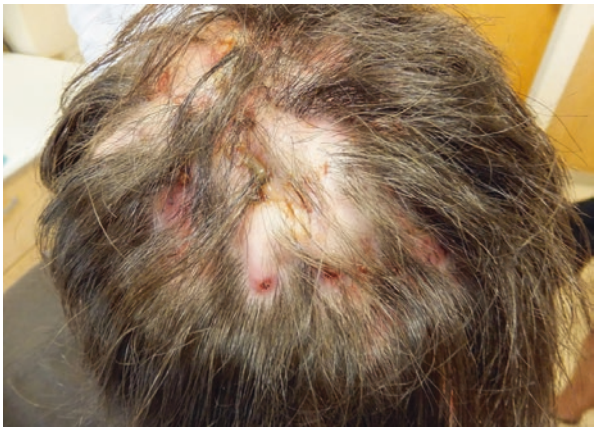

Fig. 14.1 Multiple draining nodules along with alopecia on the central and posterior scalp. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

Diagnosis

Dissecting cellulitis.

Discussion

Dissecting cellulitis of the scalp (DCS), also known as Hoffman disease and perifolliculitis capitis abscedens et suffodiens, is a rare and likely underreported dermatologic condition characterized by draining sinuses and pustules leading to primary cicatricial alopecia. The most affected group are young African American men, aged 20–40 years, but the disease has been reported in women and other racial groups as well [1]. It is hypothesized that hormones may play a role in the disease process due to the presentation of the disease on the vertex of the scalp in young men. Additionally, there is some evidence of DCS among families, proposing a potential genetic predisposition [2].

The initial presentation of DCS is commonly one or more papules or pustules at the vertex of the scalp. Left untreated, these pustules develop into boggy nodules that form sinus tracts to other lesions [3]. Patients often report flares of symptoms with itching, pain, and foul odor being common complaints. As the disease progresses, patients may notice hair loss at the side of nodules. The cause of DCS is not well understood but it is thought to be partially caused by hyperkeratosis leading to follicular occlusion. This pressure can lead to rupture, chronic inflammation, and secondary bacterial infection. The most commonly implicated bacteria in secondary infections are *Staphylococcus aureus* species and treatment should be appropriately tailored.

Three other diseases follow similar pathology and are collectively referred to as the follicular occlusion tetrad: hidradenitis suppurativa (HS), acne conglobata (AC), pilonidal sinus, and DCS [4]. The pathophysiology of these conditions is believed to be caused by follicular keratosis and occlusion in apocrine-bearing areas, leading to the characteristic painful and malodorous inflammatory nodules and abscesses [5]. As the follicles rupture and re-epithelialize, fistulas and draining sinus tracts can form [6]. The chronic, relapsing, and remitting nature of the tetrad predisposes affected individuals to the development of secondary bacterial infection, disfiguring scars, and subsequent cicatricial alopecia [5]. The symptom complex shares these characteristics and diagnosis remains largely clinical, highlighting the importance of distinguishing the follicular occlusion tetrad from other inflammatory disorders. When the lesions are found in intertriginous areas, it is classified as hidradenitis suppurativa. When on the face, shoulders, arms, or thighs it is termed acne conglobata. Lesions in the gluteal cleft are pilonidal disease and of the scalp, DCS. Microscopy may help distinguish DCS from other diseases of the scalp. The histopathology of DCS will vary with stage. In earlier stages, lesions demonstrate dense neutrophilic predominance with associated lymphocytic, histiocytic, and plasmacytic infiltrates.

As the inflammation progresses to a more chronic state, lesions contain granulomas consisting of lymphocytes, plasma cells, and foreign-body giant cells [7]. Given the similarity in disease pathology, it is estimated that up to one-third of patients with DCS have concomitant hidradenitis suppurativa or acne conglobata.

Further, studies have demonstrated that these patients are at an increased risk of developing an HLA-B27-negative spondylopathy [8]. Joint pain usually presents after the onset of cutaneous findings with the waxing and waning nature of DCS, HS, and AC flares. The association between DCS and inflammatory arthritis is poorly understood but current literature suggests a potential hypersensitivity to sebum, skin antigens, or bacterial antigens as the inciting factor. This hypothesis is further supported by positive ANA and symptom improvement after corticosteroids [9]. DCS may present with other inflammatory disorders including arthritis, keratitis, pyoderma gangrenosum, and Crohn's disease [10]. Potential complications of untreated or recalcitrant disease include osteomyelitis and metastatic squamous cell carcinoma, necessitating thorough, regular evaluation and treatment in all patients presenting with progressive DCS [11].

Oftentimes, a diagnosis of DCS is made based on clinical features alone. However, exudative cultures are recommended to rule out co-existing bacterial or fungal infections. In indeterminate cases, dermoscopy presents a useful diagnostic tool. Early disease is characterized by visualization of empty follicular openings with yellow and black dots versus end-stage disease where confluent white areas without follicular openings are present [12]. Lastly, a punch biopsy of a boggy or actively inflamed nodule may provide useful diagnostic information prior to the initiation of treatment.

Treatment

Treatment of DCS can be difficult as there is no established gold standard and cases often become refractory over time. The goals of therapy are to prevent follicular occlusion, reduce inflammation, and decrease the risk of developing secondary infections. For all patients, appropriate counseling on the relapsing and remitting nature of the disease is paramount. Particular attention should be paid to the psychosocial implications, as many patients seek initial evaluation out of concern for foul odor and alopecia. Currently, there is no agreed upon staging scale for DCS.

Clinicians can best stratify their patients' disease based on the number and size of lesions, amount of drainage, and scarring present at the time of diagnosis. In mild cases, treatment options include a combination of scalp hygiene, topical antiseptics, topical or oral antibiotics, incision and drainage, and corticosteroid injections [3]. Scalp hygiene, including benzoyl peroxide wash, chlorhexidine, or other antimicrobial soaps, are reasonable first treatments. Steroid treatment can include intralesional triamcinolone 10–40 mg/cc or oral prednisone 40–60 mg/day [7]. The dosing of triamcinolone should be tailored to the degree of inflammation; high doses may be beneficial in the treatment of keloidal scarring.

Given that the majority of DCS lesions are colonized by *S. aureus*, treatment should be tailored with adequate antimicrobial coverage. The preferred first-line

oral antibiotics are ciprofloxacin 250–500 mg BID or combination clindamycin 300 mg twice daily and rifampin 300 mg twice daily, with recommended use for at least three months [7]. Additional agents include tetracyclines and TMP-SMX. If alternative colonization is expected, exudative cultures are recommended prior to initiation of antibiotics.

Oral isotretinoin presents another option and is frequently used in more severe cases or when the aforementioned agents have failed. A meta-analysis by Guo et al. showed that oral isotretinoin is an effective treatment for improving symptoms of the disease, however, 24% of patients experienced symptom recurrence after discontinuation of therapy [13].

Alternatively, 5-aminolevulinic acid photodynamic therapy (ALA-PDT) has demonstrated promising results as a non-invasive and safe therapy for DCS [14]. Photodynamic therapy acts by using a drug as a photosensitizer to destroy affected tissue when activated by visible light [15]. However, patients should be appropriately counseled prior to initiating therapy, as ALA-PDT has not demonstrated the ability to promote hair regrowth.

Given its recent success in the treatment of hidradenitis suppurativa, the use of TNF-α inhibitors can be employed in severe DCS as well. Adalimumab specifically has been shown not only to have efficacy in severe cases of DCS, but also to stimulate hair regrowth [16]. While these agents provide varying levels of improvement, a certain subset of patients may experience refractory symptoms necessitating surgical excision. Both staged excision of sinus tracts and scalpectomy with split-thickness grafting have been reported with good success [4, 17]. Patients should be counseled on the permanent nature of hair loss after scalpectomy and offered psychosocial support if needed.

Key Points

- Dissecting cellulitis of the scalp (DCS) is a rare condition characterized by boggy nodules and draining sinuses that can lead to permanent scarring and hair loss.
- The pathophysiology of DCS is incompletely understood but thought to be related to follicular occlusion and secondary bacterial infection leading to sinus tract formation.
- A variety of treatments are available for DCS with varying efficacy. Antibiotics and isotretinoin are first-line agents, but new advances in treatment include photodynamic therapy and immune modulators.

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22-Year-Old Male with Firm, Itchy Papules, and Hair Loss on the Occipital Scalp

15

Ryan Jay, Austin Cusick, Suchita Sampath, and Shannon C. Trotter

Abstract

Acne keloidalis nuchae (AKN) is a rare cicatricial alopecia that typically affects young African-American males. While the pathophysiology is not well described, there are several competing theories to explain the phenomenon including foreign body reactions to hair, lichen simplex chronicus, or a subtype of acne mechanica. The most accepted pathophysiology involves chronic folliculitis in genetically susceptible patients that is exacerbated by excoriations and continued inflammation. Diagnosis of AKN is usually clinical, and presentation is often described in stages from the nape of the neck to the vertex of the scalp. Physical exam will reveal papules and pustules of various sizes that may coalesce into plaques. These lesions can be accompanied by excoriations. There may also be overlying signs of bacterial infection secondary to trauma. Severe manifestations will be characterized by large smooth plaques that extend beyond the borders of the original pathology. While not required, dermoscopy and histopathology can help diagnose AKN. No standardized treatment regimen currently exists for AKN. The primary focus should be placed on preventing further trauma to preexisting lesions. Moreover, antibacterial cleaners can be useful in reducing bacterial burden and subsequent infection. In early stages, treatment can begin with topical corticosteroids. Intralesional triamcinolone can be used for larger papules and plaques. Other potential medications include topical retinoids, topical clindamycin, or systemic tetracyclines. AKN characterized as "tumor stage" may

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_15

require surgical intervention, and several approaches exist. The primarily described approach includes horizontal elliptical excision with healing by secondary intention. This treatment has been expanded upon to include possible staged excisions utilizing skin grafts or varying excision approaches including the occipital protuberance. Breakthrough papule formation can be treated with high potency topical corticosteroids or intralesional steroids. Treatment of AKN largely depends on the physical presentation and desired cosmesis.

Keywords

Acne keloidalis nuchae · Cicatricial alopecia · Chronic folliculitis · Spade sign

A 22-year-old male presented with several hard papules on the occipital scalp of 9 months duration that started after he entered basic training for the army. He admitted to scratching at the lesions constantly. Some of the papules seemed to come and go, but most were constant and lacked hair growth.

On physical examination, there were firm papules and areas of scarring alopecia noted on the occipital scalp with few scattered pustules (Fig. 15.1). The rest of the scalp was spared. The eyebrows and eyelashes were of normal density. The fingernails were normal.

Based on the clinical case description, what is the most likely diagnosis?

1. Tinea capitis
2. Dissecting cellulitis
3. Acne keloidalis nuchae
4. Folliculitis decalvans

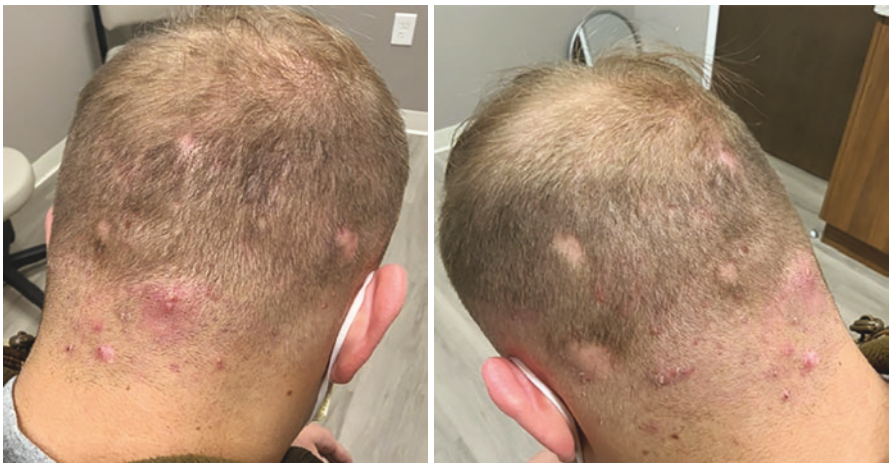

Fig. 15.1 Areas of scarring alopecia along with scattered pustules and multiple firm papules along the occipital scalp

Diagnosis

Acne keloidalis nuchae.

Discussion

Acne keloidalis nuchae (AKN) is a rare and chronic scarring (cicatricial) alopecia involving the hair follicles that predominantly affects post-pubertal men of African descent under 55 years of age [1]. The incidence ranges between 0.45% and 9%, with most cases in populations with darker skin and curlier hair [2]. Risk factors and associated conditions linked to AKN include obesity, hypertension, chronic scalp folliculitis, pseudofolliculitis barbae, increased frequency of hairdressing, and close hair cropping [3, 4].

Though the name suggests it encompasses keloids or acne, AKN is not characterized by true forms of either one. The pathophysiology is not entirely known and may be multifactorial, but several hypotheses have been postulated without significant support. These include AKN as a transepithelial elimination disorder stemming from a foreign body reaction to misplaced hair, lichen simplex chronicus with scarring, a foreign body reaction to ingrown hairs, and a variation of acne mechanica. The more widely accepted pathophysiology is chronic folliculitis from rubbing, scratching, or irritation to the occiput and nape that leads to scarring [5]. Diagnosis is usually clinical, and the presentation may appear variably based on the stage of lesions. Often preceded by pruritus, the onset of AKN presents anywhere from the nape of the neck to the vertex of the scalp with various-sized papules or pustules that may coalesce. Active areas may bleed, itch, or feel painful. Subsequent manipulation by the patient could induce a secondary bacterial infection. Chronic irritation then leads to keloid-like nodules and plaques with alopecia [1] (Fig. 15.2). Dermoscopic findings may include perifollicular pustules, perifollicular fibrosis, or tufted hairs are found [6]. Histopathology does not offer specific findings outside of

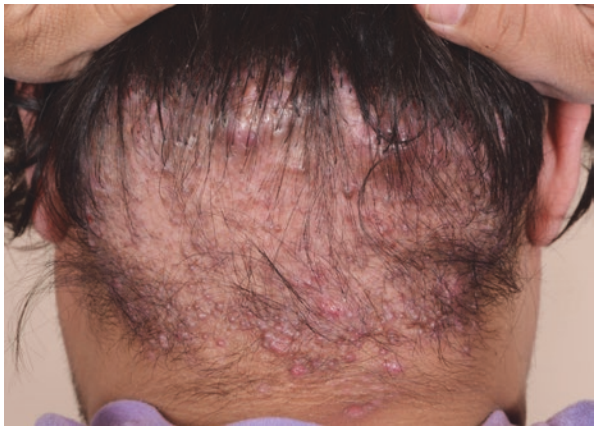

Fig. 15.2 Various sized papules and pustules along the nape of the neck. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

features common to other scarring alopecia, such as perifollicular inflammation with lymphocytes and plasma cells, peri-isthmic lamellar fibrosis, and absent sebaceous glands [7]. However, recently, a pathognomonic finding during the subacute stage of AKN was proposed [8]. The finding is called a "spade sign" and describes the inflammation leading to a dilated spade-like space in the lower isthmus of hair follicles [8].

Treatment

AKN is difficult to manage because no widely accepted treatment regimen exists. Numerous measures from case series have reportedly helped with varying degrees of success. Efficacy of treatment depends upon the stage and extension of lesions, with multimodal approaches often working the best. First and foremost, preventative measures must be taken to combat mechanical irritation. This includes wearing non-irritative clothing or collarless shirts and avoiding close shaving of the occiput and nape of the neck. Antibacterial cleaners may also be implemented in the treatment of secondary infections [2]. In the earlier stages where only small papules and no keloid-like scars are present, treatment often begins with topical corticosteroids to the affected region and intralesional triamcinolone for larger papules and plaques [1]. Simultaneous topical retinoids for mild disease or topical clindamycin for pustular presentations may be utilized with corticosteroids. In more extensive mild-to-moderate cases, systemic tetracyclines may also be used for anti-inflammatory and antibacterial properties [9].

Severe or later-stage cases that are resistant to medical therapies and present with large keloid-like nodules and plaques may consider surgery. Surgical excision with a horizontal ellipse involving the posterior hairline and healed by secondary intention led to resolution and favorable cosmetic results [10, 11] (Fig. 15.3). However, others found success with a multi-faceted surgical technique. Galarza et al. treated giant 'tumor stage' AKN with radical surgical excision and initial secondary intention healing for 50 days, which allowed the wound to contract and heal before utilizing a skin graft [12]. In an intervention before-after trial of 25 patients undergoing surgical excision for refractory AKN, little risk of recurrence was found for cases with primary closure (though not as favorable in cosmesis), and those with especially large lesions responded well to a staged-excision approach [13]. An innovative and successful surgical method by Umar et al. utilized a bat-shaped excision of affected areas confined to the occipital protuberance superiorly and the posterior hairline inferiorly, followed by secondary intention healing with or without tension suture assistance [14]. If minimal recurrence of papules or pustules happened after surgical excision, high potency topical steroids and intralesional steroids usually resolved them [13]. Overall, providers should decide on a surgical approach based on the severity of the case and desired cosmetic outcome.

Laser hair removal represents another potential treatment for AKN. Long-pulse, long-wavelength lasers are preferred because they can better penetrate the

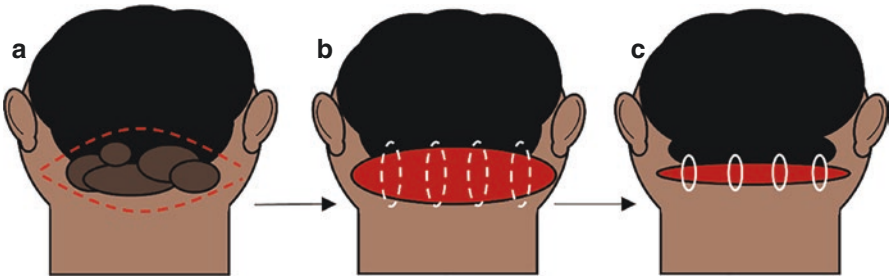

Fig. 15.3 Surgical procedure with a horizontal ellipse for severe AKN. Panel **a** depicts AKN and the red dotted line depicts an elliptical excision pattern. Panel **b** demonstrates the surgical defect and placement of tension sutures (white dotted line). Panel **c** shows the final product of tension sutures with partial closure allowing the remaining defect to close by secondary intention

2–4 mm average depth of follicles [14]. 1064 nm Nd-YAG may theoretically work the best because it has the deepest penetration while damaging melanocytes the least [15]. A comparative study between Er:YAG and Nd:YAG lasers found that both led to a significant decrease in the number of papules, as well as the size and consistency of plaques [16]. Similarly, a study with 17 patients utilized 6 sessions of 755 nm alexandrite laser therapy and demonstrated a significant improvement in mean papule/pustule count, plaque size, and pliability of lesions [17]. A combination of lasers with other treatment modalities, such as Nd-YAG with topical corticosteroids or excision followed by Nd-YAG, can be personalized for severity, and may provide a more favorable outcome [18, 19]. For those who are neither surgical nor laser candidates, or have remained refractory to all the aforementioned treatments, low-dose radiotherapy may lead to resolution [20, 21].

Treatment of AKN depends on the type, size, and extent of lesions, and multimodal approaches are often needed. Patients should also be counseled on the difficulties of AKN management and treatment. Initially, preventative measures should be implemented followed by progressively invasive therapies as needed.

Key Points

- Acne keloidalis nuchae (AKN) tends to affect post-pubertal men of African descent with curly hair, though other demographics can be afflicted too.
- Early lesions can present on the occiput and nape as small papules and pustules, but later stages present as larger keloid-like nodules and plaques.
- Treatment begins with topical and intralesional corticosteroids with or without systemic tetracyclines, while later staged or severe disease may require surgery.
- Laser hair removal done at earlier stages may be an effective treatment that prevents future occurrences.

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82-Year-Old Female with Crusted, Eroded Plaques the Central Scalp

16

Daniel Hyman, Trent Walker, Suchita Sampath, and Shannon C. Trotter

Abstract

Erosive pustular dermatosis (EPD), as its name suggests, is characterized by pustules and erosions clustered together. The most common distributions are localized to either the scalp or the legs. Most individuals are older, although rare cases have been reported in children. Diagnosis may be delayed due to overlap with actinic damage and infection. Diagnosis is generally made through a combination of biopsy, treatment failure, and therapy response. Histopathology may show a neutrophilic pustular inflammatory process, leading many to categorize EPD as a neutrophilic dermatosis. The etiology is still unknown, but trauma of any means tends to be a common preceding factor. Treatment is most commonly with topical steroids. Many other proposed treatments are mentioned in the literature. Prognosis is generally good, and many patients achieve long-term resolution of EPD.

Keywords

Erosive pustular dermatosis · EPDS · Cicatricial alopecia · Corticosteroids · Photodynamic therapy · Tacrolimus

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_16

An 82-year-old female presented with scattered eroded plaques and pustules on the scalp for 2 months. She reported hitting her head on a car door a week around the time the eruption started. Her history was significant for actinic keratoses on the scalp and a squamous cell carcinoma on the left frontal scalp that was treated successfully with Mohs surgery.

On physical examination, there were green to yellow crusted plaques that revealed red, friable skin underneath the central scalp (Fig. 16.1). The rest of the scalp exhibited actinically damaged skin. The eyebrows and eyelashes were of normal density. The fingernails were normal. A skin biopsy showed thinning of the epidermis with partial erosion and necrosis. There was a mixed dermal infiltrate of lymphocytes, neutrophils, and a few plasma cells. A reduction of hair follicles was present. Direct immunofluorescence was negative.

Based on the clinical case description, what is the most likely diagnosis?

1. Mucous membrane pemphigoid
2. Dissecting cellulitis
3. Erosive pustular dermatosis
4. Tinea capitis

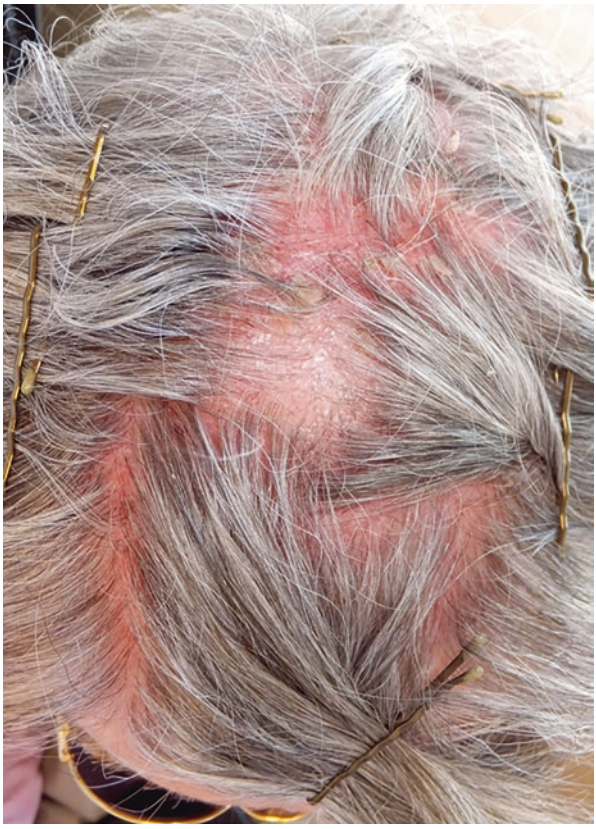

Fig. 16.1 Erythematous, friable skin present on the central scalp. Green-yellow crusted plaques are also present. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

Diagnosis

Erosive pustular dermatosis.

Discussion

First described in 1979, erosive pustular dermatosis (EPD) is a condition that appears as extensive areas of erosion with numerous scattered pustules overlying the affected region [1, 2]. Other names include erosive pustulosis and erosive pustular dermatosis of the scalp (EPDS), due to it classically involving the scalp [3]. EPD is most commonly located on the scalp or the legs of older individuals. There are contradictory reports in the literature regarding the prevalence in men versus women, although the consensus is that elderly women have the highest incidence and prevalence [4, 5]. The overall incidence and prevalence of EPD is hard to estimate because the disease is most likely under/misdiagnosed and under-reported [6].

EPDS is classically associated with trauma or pathergy to the afflicted region prior to development of the lesion. The most common trauma is actinic damage on the scalp of older individuals [6]. However, there are many reports of other traumatic associations, such as inflammatory or iatrogenic sources. These include surgery, topical therapies, systemic medications, and inflammatory diseases. Interestingly, surgical studies have determined that skin grafting may have the highest association with EPDS compared to other methods of closure [7]. Photodynamic therapy has also been considered a provoking factor, while also being described as a treatment modality [8, 9]. Thus, the etiology of EPDS is still very unclear.

EPDS generally presents as a large, poorly defined erythematous to eroded plaque on the vertex of the scalp. Pustules throughout the plaque often leave behind crusting [4]. The appearance can be similar to diffuse actinic damage on the scalp. Differential diagnosis includes actinic keratoses, squamous cell carcinoma, pemphigus foliaceus, and kerion formation [10]. While there may or may not be symptoms associated with the plaque, the most common symptoms include itching and burning [1]. EPDS is generally a scarring alopecia thought to be caused by regression of the plaque over time, leading to a loss of hair follicles [11]. Dermoscopy, or more appropriately trichoscopy, shows loss of the follicular ostia, dilated vessels, and hyperkeratosis [12]. Histopathological evaluation of the plaque can vary. EPDS can present as a neutrophilic, pustular folliculitis with features of spongiosis, but the presence of plasma cells and lymphocytes may be important in making the diagnosis [4, 13]. Histopathology is key in distinguishing EPDS from other scarring alopecias and conditions. Although there may be a background of actinic damage, there will not be evidence of actinic keratoses or squamous cell carcinoma. It is important to diagnose EPDS as early as possible to avoid irreversible damage. An early biopsy is important for many types of scarring alopecias as it provides cues to diagnosis and treatment.

Treatment

Treatment of EPDS is typically potent topical steroids with or without occlusion [5]. Oftentimes, this treatment helps support the diagnosis when histopathology and clinical features alone are not enough to make the diagnosis [14]. Regrowth of hair has been reported to occur but is not common [15]. Even though steroids are considered very effective for EPDS, there are many other treatment options available. If the patient has a history of herpes zoster on the scalp or head and neck region, topical steroids may not be the best option for treatment. There have been reports of reactivation of herpes zoster involving treatment of EPDS with chronic topical steroid use [16].

Other treatment modalities, reported in various case reports, have been noted to be effective for EPDS. These include non-steroidal immunosuppressive therapies such as topical tacrolimus [5]. The use of sulfasalazine in combination with a 308-nanometer excimer laser was successful in one case [17]. Topical zinc oxide has been reported for treatment of the leg, with a recent report indicating effectiveness for the scalp [18, 19]. As mentioned earlier, photodynamic therapy (PDT) is reported both as a cause and a treatment of EPDS. Case reports have combined PDT with surgical silicone gel or the fractional 1927 nanometer Thulium laser with effectiveness [20, 21]. Tetracycline antibiotics, oral retinoids, and oral Janus kinase inhibitors are examples of systemic agents that have also been used to treat EPDS [22–24].

Due to the unclear etiology of EPDS, no treatment modality can be universally recommended for the condition. Currently, first-line therapy for patients without contraindications is potent topical steroids. No randomized controlled trials regarding EDPS have been conducted. Future therapies may involve topical tacrolimus, sulfasalazine, topical zinc oxide, and PDT. As there is currently little evidence supporting these therapies, further testing must be performed.

Key Points

- Erosive pustular dermatosis (EPD) is rare and presents as chronic, eroded plaques with an overlying crust that cause a scarring alopecia when located on the scalp.
- The cause of EPD is most often caused by preceding trauma, such as actinic damage.
- EPD of the scalp is generally treated with topical steroids but some case reports suggest other therapies such as PDT, topical tacrolimus, and sulfasalazine may be effective.

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16-Year-Old Male with Pink Scaly Patches with Papules and Hair Loss

17

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Abstract

Alopecia mucinosa is a rare condition associated with follicular papules created by mucin deposition leading to hair loss. There appears to be no predilection for gender or age. Most commonly it presents as an idiopathic condition. However, it has been found to be associated with malignancies and inflammatory conditions, including mycosis fungoides and systemic lupus erythematosus. A biopsy will show mucin within the hair follicle and a lymphocytic infiltrate, which can aid in the diagnosis of associated conditions. Although spontaneous remission may occur, several treatment options are available that target the inflammatory nature of this condition. Treatment strategies vary depending upon disease severity and include corticosteroids for limited active disease, hydroxychloroquine, and antibiotics for moderate disease, and cyclosporine for severe disease have shown variable success rates. Janus kinase (JAK) inhibitors are being studied for lymphocytic cicatricial alopecias. Long-term follow-up is essential to evaluate for the development of secondary conditions.

Keywords

Alopecia mucinosa · Cicatricial alopecia · Follicular mucinosis · Corticosteroids · Photodynamic therapy

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_17

A 16-year-old male presented with a pink, scaly patch on the scalp and forehead. The lesion on the scalp lacked hair. The lesions had been present for around 8 months. He received a course of oral terbinafine for 2 months with no improvement. He denied hair loss elsewhere on the body.

On physical examination, there were two pink scaly patches observed with follicular papules, one on the posterior scalp with hair loss and one on the left forehead. Eyebrows and eyelashes were of normal density. The fingernails were normal. A skin biopsy showed mucinous degeneration of the hair follicles and perifollicular lymphocytic inflammation with no atypical cytological features. The overlying epidermis showed no significant abnormalities.

Based on the clinical case description, what is the most likely diagnosis?

1. Alopecia mucinosa
2. Seborrheic dermatitis
3. Alopecia areata
4. Discoid lupus erythematosus

Diagnosis

Alopecia Mucinosa.

Discussion

Alopecia mucinosa is a rare type of lymphocytic primary cicatricial alopecia that presents with follicularly based papules and scaly plaques with subsequent hair loss. Alopecia mucinosa can affect patients at any age and involve any part of the body [1]. It tends to affect the head and neck, especially the scalp and eyebrows [1]. Clinically, alopecia mucinosa presents as follicular papules with or without erythematous scaly plaques and associated loss of hair [2]. There can be multiple well-defined, indurated plaques with patulous follicular ostia, seen best with dermoscopy [3]. The papules are grouped and can be associated with pruritus [4]. Less commonly, alopecia mucinosa may present morphologically similar to follicular cysts or keratosis, alopecia areata-like patches, dermatitis, urticaria, or acneiform lesions [5].

The terms alopecia mucinosa and follicular mucinosis are used synonymously and interchangeably in the literature. Follicular mucinosis refers to the nonspecific deposition of mucopolysaccharides such as mucin within the hair follicle [6]. Follicular mucinosis is a pattern of epithelium that can present in many disease states and alopecia mucinosa is an inflammatory disease that can present with follicular mucinosis [7].

Alopecia mucinosa can be separated into three classifications based on the presentation and course. First, there is a primary, acute form of alopecia mucinosa that is an idiopathic and spontaneous or remitting type seen in children and young adults

[8]. Second, there is a primary, chronic relapsing type seen in older adults [8]. Third, there is secondary alopecia mucinosa associated with malignancies and inflammatory conditions [8]. The most common malignancy associated with secondary alopecia mucinosa is cutaneous T-cell lymphoma, specifically mycosis fungoides [8]. Other associated malignancies that have been documented include Hodgkin's lymphoma, chronic lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and leukemia cutis [8]. The malignancy may be diagnosed before, along with, or after the diagnosis of alopecia mucinosa [6, 8]. Secondary alopecia mucinosa is also associated with several inflammatory conditions such as lupus erythematosus, sarcoidosis, alopecia areata, and lichen simplex chronicus [8].

Histologically, alopecia mucinosa is characterized by mucinous degeneration of the outer root sheath until the entire pilosebaceous unit is replaced by pools of mucin [9]. Mucin accumulation can cause swelling of the follicular epithelial cells and loss of intracellular bridges [8]. The mucin is made of hyaluronic acid, secreted by follicular keratinocytes [10]. The mucin can be stained by colloidal iron or alcian blue [8]. A lymphocytic infiltrate can be found in the follicular, perifollicular, and perivascular areas and diffusely in the dermis [8, 9].

Although alopecia mucinosa can frequently be diagnosed based on clinical features alone, a biopsy is recommended for confirmation. Alopecia mucinosa is often associated with cutaneous T-cell lymphoma, especially in elderly individuals, and further diagnostic testing of biopsies such as staining, and immunohistochemistry should be performed to rule out malignancy [4]. Long-term follow-up and serial biopsies are recommended since malignancy can coincide with or follow alopecia mucinosa [4, 6].

Treatment

There is no standard therapy available for alopecia mucinosa [4]. The key to any scarring alopecia is early control of the underlying disease to prevent permanent hair loss and reduction of symptoms. Treatment approaches are aimed at suppressing inflammatory processes and early treatment halts disease progression and allows for the possibility of scalp hair regrowth [11]. Treatments are grouped into three tiers based on increasing severity [11]. Tier 1 treatments are for patients with limited active disease. Treatment options include topical high-potency corticosteroids, intralesional steroids, or topical nonsteroidal anti-inflammatory creams such as tacrolimus or pimecrolimus [11]. Tier 2 treatments are for patients with moderate disease. Treatment options include hydroxychloroquine, low-dose oral antibiotics, or acitretin [11]. Tier 3 treatments are for patients with severe disease and include cyclosporine, prednisone, or mycophenolate mofetil [11]. Topical or intralesional corticosteroids, as well as phototherapy and superficial radiotherapy, can be used [2, 12]. A recent case study demonstrated the use of tacalcitol before and during photodynamic therapy for follicular mucinosis to remove follicular hyperkeratosis, reduce inflammation, and enhance the penetration of 5-aminolevulinic acid into the skin for effective photodynamic therapy [13]. Other options include dapsone, isotretinoin,

and minocycline [2, 8, 9]. Janus kinase (JAK) inhibitors such as the pan-JAK inhibitor, tofacitinib, are a recent novel treatment option for lymphocytic cicatricial alopecias [11, 14]. These treatments have variable success rates and placebo-controlled trials have yet to be conducted. Spontaneous remission may occur after months or years [4, 6]. Alopecia may or may not be permanent depending on the damage to follicular stem cells and the degree of mucin deposition in the pilosebaceous units [15].

Key Points

- Alopecia mucinosa is a rare type of lymphocytic primary cicatricial alopecia that can be associated with mycosis fungoides or other malignancies and inflammatory conditions.
- Alopecia mucinosa presents as follicular papules most commonly on the scalp and eyebrows that can lead to scarring alopecia.
- Treatment of alopecia mucinosa includes intralesional or topical corticosteroids, antibiotics, immunosuppressive medications, phototherapy, and superficial radiotherapy with variable success rates.

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12-Year-Old-Girl with a White Indented Plaque of the Frontal Scalp and Forehead

18

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Abstract

Morphea, or localized scleroderma, encompasses several skin conditions manifesting with sclerotic changes secondary to an idiopathic, autoimmune, inflammatory process. En coup de sabre, or "by the touch of the sword," is a form of localized linear scleroderma that affects the frontoparietal scalp and face and can result in secondary scarring alopecia. This type of morphea affects the dermal and subcutaneous layers but can extend to bone, sometimes affecting adjacent ocular and central nervous tissue. Morphea is a clinical diagnosis, initially presenting with inflamed edematous and erythematous patches before ultimately sclerosing to form bound-down indurated nodules or plaques. Unclear cases can be confirmed with a punch biopsy or a deep excisional biopsy. When morphea extends beyond the dermis, the extent of involvement should be evaluated with MRI or ultrasound. Without suspicion for other autoimmune conditions, testing for autoantibodies is not warranted given the low prognostic significance. Morphea treatment is based on how active and severe the condition is. Inactive disease lacks erythema, edema, peripheral induration, lesion expansion, or new lesion formation and can be managed with physical or occupational therapy and plastic surgery. Mild active disease can be managed with topical clobetasol, tacrolimus, vitamin D analogues, intralesional corticosteroids, and medium dose UVA phototherapy. Severe rapidly progressing morphea can be managed with

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_18

methotrexate and systemic glucocorticoids. Refractory morphea can be managed with mycophenolate, cyclophosphamide, rituximab, abatacept, and tocilizumab.

Keywords

Morphea · Scleroderma · En coup de sabre · Autoimmune · Alopecia · Methotrexate Corticosteroids · TGFβ

A 12-year-old female reported a two-year history of a firm, white plaque that evolved on her scalp and forehead. The area on the scalp lacked hair and appeared depressed. Her mom reported that the area initially looked like a dark brown line, and they were told it was a birthmark (Fig. 18.1). The patient's medical history was significant for headaches and decreased visual acuity. She recently was fitted for new glasses. The patient was in distress over the cosmetic appearance of her skin and the hair loss, which prompted her evaluation.

On physical examination, a linear, indurated white, hairless plaque was observed extending from the frontal scalp into the central forehead. Eyebrows and eyelashes were of normal density. The fingernails were normal. The remaining skin exam was normal. A biopsy was performed and demonstrated thickened, hyalinized collagen bundles in the reticular dermis and subcutis. There was trapping of eccrine glands within the middle of a thickened dermis and a decreased number of adnexal structures and blood vessels.

Based on the clinical case description, what is the most likely diagnosis?

1. Alopecia areata
2. Dissecting cellulitis
3. Morphea
4. Tinea capitis

Fig. 18.1 Depressed, hyperpigmented patch on the forehead extending into the scalp. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

Diagnosis

Morphea

Discussion

Morphea, otherwise known as localized scleroderma, encompasses a group of skin diseases that present with sclerotic skin changes secondary to an idiopathic, inflammatory process [1, 2]. The five types of morphea include bullous, plaque, generalized, deep, and linear [3]. Localized scleroderma should not be confused with systemic sclerosis, which can affect internal organs without affecting the skin [4]. Unlike systemic sclerosis, morphea lacks sclerodactyly, nailfold capillary changes, and Raynaud's phenomenon [2]. Morphea has been shown to impact 3–27 individuals per 100,000 with women affected at a ratio 2.4–5 times greater than men [2]. Although the disease can affect patients at any age, it has a bimodal distribution with peaks around 7–11 and 44–47 years of age [2]. Alopecia secondary to morphea is often associated with en coup de sabre, a localized linear scleroderma that affects the frontoparietal area of the scalp as well as the face [5]. En coup de sabre presents as a white, linear, depressed, indurated, atrophic plaque with scarring alopecia [6]. It often resembles a scar from the strike of a saber or sword. The morphea of en coup de sabre affects the dermis and subcutaneous connective tissues but can also involve the muscles, cartilage, and bone, sometimes affecting the ocular and central nervous systems below the cutaneous lesions [3, 6]. Patients with morphea present with one or more plaques that are typically active for 3–5 years, although sometimes plaques can be more persistent [2, 7]. Unfortunately, even after active disease subsides, hyperpigmentation, contractures over joints, and atrophy can lead to persistent mobility impairment and disfigurement [1, 4]. Moreover, the course is relapsing and remitting, with about a 25% relapse rate, even after years of quiescence [8].

Morphea is diagnosed clinically, with the history and physical exam resting as the cornerstones of the diagnosis [2]. Distinguishing morphea from systemic sclerosis is of paramount importance when making the initial diagnosis [7]. Initially, inflammatory morpheaform lesions present as edematous, inflammatory, erythematous patches and plaques that can be pruritic or painful [2]. Next, sclerosis expands from the center of the lesions, surrounded by an erythematous or violaceous border, before ultimately manifesting as bound-down, indurated nodules or plaques [2, 7]. Sclerotic lesions may result in the malformation, damage, or destruction of pilosebaceous units leading to cicatricial alopecia [9]. However, after months to years, the sclerotic lesions transition into softer, dyspigmented atrophic plaques associated with the inactive phase of the disease [2]. Deep, linear morphea is typically unilateral and can result in limb-length discrepancies in children [2]. When suspecting linear scleroderma, providers should evaluate the patient for signs of systemic sclerosis, such as Raynaud's phenomenon, sclerodactyly, and capillary nail fold changes

[7]. Histopathologic examination of biopsies and laboratory tests are not necessary in a majority of morphea diagnoses [2]. A skin biopsy should only be considered in cases of unclear patient presentation of morphea [2] In cases of deep morphea beyond the dermis, MRI should be used to evaluate soft tissue involvement and lesion depth and monitor musculoskeletal involvement [2]. Ultrasound is the preferred imaging modality to monitor disease activity in superficial morphea [2] Since the prognostic significance of autoantibodies is unclear, testing for them is not recommended [2].

While the cause of morphea is idiopathic, factors such as epigenetics, autoimmunity, and vascular dysfunction have been shown to play a role in its pathogenesis [2, 10]. Despite a lack of a particular gene being involved in morphea development, strong associations were found with the HLA class I allele HLA-B*37A and HLA Class II allele DRBI04:04 [2]. Additionally, patients with morphea are more likely to have a family history of autoimmunity [7]. Currently, no morphea-specific antibodies have been discovered [2]. Early morphea lesions have been shown to be teeming with mononuclear lymphocytes such as T lymphocytes, eosinophils, and plasma cells [2, 10]. Samples of affected skin have shown decreased dermal capillaries, irregularities in blood vessel basal lamina, and damaged endothelial cells, findings which point to vascular dysfunction as a component of localized scleroderma generation [7, 10]. The mechanism likely involves the activation of $CD4^+$ T_H2 cells, which secrete interleukin-4 (IL-4), subsequently activating T lymphocytes to secrete transforming growth factor ß (TGF- ß) [10]. The excess of TGF-ß stimulates fibroblasts to produce collagen and extracellular matrix proteins, directly contributing to sclerosis [10]. During the inflammatory phase, vascular endothelial damage triggers the release of cytokines that stimulate vascular adhesion molecule expression [7, 10]. Specific adhesion molecules that have been detected at higher levels in the serum of morphea patients include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin [7, 10]. Tissue damage also results in the secretion of chemokines, attracting leukocytes to extravasate into the dermis [3]. Subsequently, the lymphocytes produce profibrotic cytokines including IL-1, IL-4, IL-6, IL-8, IL-13, and TGF- ß, which activate fibroblasts, pericytes, and endothelial cells to differentiate into myofibroblasts [3]. The activated myofibroblasts produce collagen, fibronectin, and tenascin-c, thus activating more fibroblasts to differentiate into myofibroblasts and perpetuating the cycle of fibrosis [3].

Treatment

The treatment of morphea largely depends on disease severity and activity. Certain features are associated with active, inflammatory morphea, including erythema, peripheral induration, lesion expansion, and new lesion formation [11]. If these clinical features are absent, then the morphea is in the inactive, “burnt out” phase. Currently, therapy is considered most effective when targeting the active stage of the disease [12]. Despite the lack of current medical treatments, patients can be

referred to physical therapy or occupational therapy if mobility is impaired due to excessively tight skin or joint contractures [13]. However, even in cases where lesions are removed or managed medically with systemic treatment, lesions can recur even several years later [14].

In cases of active morphea, treatment can be further stratified by the level of disease activity. When patients have a few active plaques without new lesion formation, then patients should undergo treatment with topicals such as corticosteroids, tacrolimus, calcipotriene, or intralesional injections of corticosteroids [15]. Adjunctive treatment with phototherapy can be considered with superficial and deep active morphea lesions [2]. In cases of rapid lesion formation or progressive deep morphea, patients should be started on long-term systemic methotrexate (12.5–25 mg/week) along with an optional prednisone bridge at 0.5 to 2 mg/kg daily for 2–4 weeks followed by a gradual taper over several months [15].

The current management recommendations are largely based on lower-quality evidence (1B-3) and there is much room for clinical trials to standardize existing or novel treatments [13]. It has been shown that methotrexate plus steroids result in superior outcomes relative to placebo plus steroids, but methotrexate plus steroids have not been shown to be superior to methotrexate alone [4, 16]. Methotrexate is well known for its role in suppressing folate metabolism by blocking dihydrofolate reductase [17]. Medium dose UVA_1 phototherapy has been shown to be more effective than narrow-band UVB in a randomized controlled trial and works by suppressing collagen synthesis [16]. Although oral calcitriol has failed to show efficacy beyond placebo, topical calcipotriene plus betamethasone showed relief in all 12 patients in one case series [18]. Vitamin D analogues have been shown to inhibit fibroblast proliferation and downregulate T cells [16].

Fortunately, several exciting novel agents may become used for morphea management in the future. The general classes of these medications fall into the categories of antifibrotics, anti-inflammatory agents, cellular and gene therapy agents, and senolytics [3]. One of the antifibrotic agents is fresolimumab, an anti-TGFβ monoclonal antibody, which has shown promise in early-stage trials in diffuse cutaneous systemic sclerosis [19]. Another similar agent is pamrevlumab, a monoclonal antibody against connective tissue growth factor (CTGF), a downstream marker of TGFβ. This drug increases vascular injury and inhibits the recruitment of inflammatory cells and fibroblasts. Currently, pamrevlumab is being tested in an ongoing trial for interstitial lung fibrosis [20].

Anti-inflammatory agents are often used for morphea because of their relative abundance. One example is the anti-IL-6 monoclonal antibody, tocilizumab, which has been shown to modestly affect skin scores in systemic morphea in a randomized clinical trial [3]. Interestingly, the PPARα agonist, fenofibrate, and the PPARγ agonist, pioglitazone, have been shown to have both anti-inflammatory as well as antifibrotic properties [3]. However, the amount of PPAR agonist activity these drugs have is high enough to raise safety concerns when used for morphea. Therefore, lanifibranor, a novel pan PPAR agonist with mild activity, was developed and has been shown to reduce skin fibrosis [3]. Lanifibranor is currently being investigated in an ongoing phase 2 trial for morphea and a phase 3 trial for NASH cirrhosis [21].

Topical crisaborole, a PDE-4 inhibitor, has been shown to decrease M2 macrophage differentiation and thus decrease skin fibrosis [3]. While crisaborole is being investigated in a phase 2 trial for morphea, there have not been any reports to date utilizing apremilast, an oral PDE-4 inhibitor, as a treatment for morphea [22]. Other well-known immunosuppressive agents that have shown efficacy in the treatment of morphea in randomized clinical trials include mycophenolate, cyclophosphamide, rituximab, and abatacept [4].

Two novel miscellaneous agents are currently in the drug pipeline that are worth mentioning. First, there is a cellular and gene therapeutic agent called FCX-013, which is a modified autologous fibroblast [3]. In the ongoing trial, this agent has been injected directly into morphea plaques and then subsequently induced by a second oral agent to express matrix metalloprotease 1 (MMP-1), thus leading to targeted collagen breakdown [3, 23]. Secondly, a senolytic agent called dasatinib, a selective BCR-ABL and SRC tyrosine kinase inhibitor, has been shown to decrease senescence-resistant myofibroblasts. Furthermore, dasatinib has shown clinical improvement in a phase 1 trial of interstitial lung disease secondary to systemic sclerosis [3].

Although methotrexate is considered first-line management in severe morphea, not all patients are able to tolerate methotrexate due to various comorbidities. In cases of hepatic insufficiency, mycophenolate may be a safer alternative, as well as being the general second-line agent behind methotrexate [24]. In cases where patients with severe morphea have renal insufficiency, rituximab may be the favored choice, followed by mycophenolate or cyclophosphamide if renal dosing is accounted for [25, 26]. In cases of heart disease, methotrexate is still considered first-line and has been shown to have cardioprotective benefits in patients with rheumatoid arthritis [27]. For patients with lung disease, cyclophosphamide may be a reasonable option as it has been shown to have modest benefits in interstitial lung disease [28]. For patients without insurance, methotrexate is an affordable first-line drug. Similarly, in cases of deep tissue and musculoskeletal involvement, methotrexate is still the first-line treatment [2]. In cases of serious infection, immunosuppressive treatment may need to be held until after the infection resolves [29]. For pregnant patients, hydroxychloroquine has been found to be both safe and effective [30]. Meanwhile, children are treated similarly to adults, albeit with dose adjustments. Although managing and studying morphea can be difficult due to its relative rarity, often self-limiting course, variety of presentations, and the relative paucity of high-quality trials, there are many new agents that have the potential to revolutionize morphea management.

Linear morphea associated with the head and neck is at significant risk to contracture and cause deformity, thus requiring aggressive systemic therapy [1]. Therapy for en coup de sabre generally starts with methotrexate and a short course of systemic corticosteroids for 2–3 months [1]. If treatment is ineffective, options such as phototherapy (PUVA, UVA, or UVA1) or mycophenolate should be considered [1].

An important aspect in the treatment of morphea is patient education on the scarring nature of the disease. Patients should be counseled that treatment is aimed at

new, active lesions and involved skin may never return to its previous appearance [1]. The chronic, inactive lesions are often unresponsive to treatment and do not warrant systemic therapy [1]. Hair transplant can also be performed in patients who have a healthy, non-scarred patch of hair [9]. Hair transplantation is not as effective in scarred tissue due to the decreased blood supply [9]. Another possible option for future hair growth includes hair autografting followed by topical minoxidil 5% [31].

Key Points

- Morphea is an idiopathic, inflammatory autoimmune cutaneous and connective tissue condition that presents as white, linear, depressed, indurated, and atrophic plaques with scarring alopecia.
- Inactive morphea is devoid of features such as erythema, edema, peripheral induration, lesion expansion, and new lesion formation and can be managed with physical therapy, occupational therapy, and plastic surgery.
- Mild active morphea can be treated with topical clobetasol, tacrolimus, vitamin D analogues, intralesional corticosteroids, and medium-dose UVA_1 phototherapy.
- Severe morphea with rapid progression can be managed with methotrexate with or without systemic glucocorticoids.
- Refractory morphea can be treated with mycophenolate, cyclophosphamide, rituximab, abatacept, tocilizumab, and newer agents as they exit the pipeline.

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60-Year-Old-Female with Hair Loss After Treatment for Reactive Lymphoid Hyperplasia

19

Richard Boyd, Gabriel Mirhaidari, Suchita Sampath, and Shannon C. Trotter

Abstract

Radiation therapy, both for treatment and diagnosis, is becoming increasingly prevalent in medical practice. Alopecia is a potential side effect that warrants substantial consideration, with many patients claiming this as the most distressing aspect of their procedure, and some even stating they would forgo curative treatment due to potential alopecia. Hair loss is typically localized to the area of treatment and occurs in a dose-dependent fashion a few weeks after exposure to radiation. In addition to the cumulative dose of radiation that a patient receives, severity of hair loss may also be increased by the method of radiation delivery, patient-related factors such as smoking, and the use of certain antineoplastic agents. Diagnosis is based on clinical presentation and a history of radiation exposure, with dermoscopy findings for lower doses being similar to that of alopecia areata. Although most cases will spontaneously resolve within 6 months, prevention and treatment options do exist for refractory cases of alopecia. Newer treatment delivery methods that reduce off-target radiation, preventative therapies, topical medications, injections, surgery, and transplantation have all been used with some success. Of note, scalp cooling has not been shown to be an effective prevention strategy in alopecia due to radiation.

Keywords

Radiation · Radiotherapy · Alopecia · Scalp cooling · Minoxidil

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_19

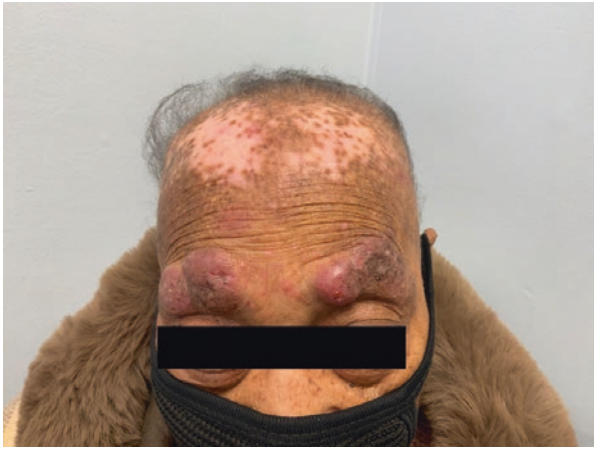

Fig. 19.1 Hypopigmented patches with scarring alopecia present on the frontal scalp. Note the presumed new areas of reactive lymphoid hyperplasia in her eyebrows

A 60-year-old female reported hair loss after her scalp was treated for reactive lymphoid hyperplasia about 5 years ago. She stated that after her treatment ended, she had a rash on the scalp for about 3 weeks that then resolved. The area healed with pigmentation changes and her hair did not grow back. Her eyelashes were not affected by treatment but she has new lesions in her eyebrows of about 6 months duration.

On physical examination, there is complete hair loss of the central and frontal scalp. There are areas of hypopigmentation and hyperpigmentation mixed with pink and white macules and plaques. Of note, there are indurated, pink plaques of the eyebrows, consistent with new areas of reactive lymphoid hyperplasia. The eyelashes are intact (Fig. 19.1). The fingernails were normal in appearance.

Based on the clinical case description, what is the most likely cause of her alopecia?

1. Intralesional corticosteroids
2. Topical imiquimod
3. Intralesional methotrexate
4. Radiation

Diagnosis

Radiation

Discussion

Radiotherapy is becoming increasingly prevalent, with over 50% of cancer patients eventually receiving some form of radiation treatment [1]. Patients also receive radiation as part of fluoroscopic procedures, such as cerebral angiography, which

can have similar adverse event profiles [2]. Although alopecia occurs less frequently after radiation exposure than after chemotherapy, its effect on a patient's quality of life can be profound [3]. In one study, almost 20% of respondents said that alopecia was the most distressing side effect of their radiation treatment, and over 10% stated they would reject curative radiation treatment if it was associated with alopecia [4].

Alopecia after radiation follows a dose-response pattern and typically begins after cumulative exposures of 2 gray (Gy) or more [5]. Initially, the hair loss is that of anagen effluvium, in which damage to actively dividing matrix cells in the anagen follicles causes shedding of dystrophic hairs [6]. At lower doses, hair loss is expected to begin 1–3 weeks after exposure and spontaneously resolve within 2–6 months. However, severe, cicatricial alopecia can result from higher dose-exposures, with a 50% probability of toxicity found to be around 43 Gy [7]. This dose may be lower in pediatric patients, with a small study showing permanent radiation-induced alopecia resulting from doses as low as 21–30 Gy [8].

The mechanism of this damage is complex, involving an inflammatory cascade triggered by irradiated skin and endothelial cells [9]. In addition to the total exposure and type of radiotherapy used (proton versus photon), the severity of hair loss can be increased by other patient-related factors such as smoking, poor nutrition, autoimmune conditions, and the use of certain antineoplastic agents [2]. Ultimately, this can result in permanent damage to epithelial stem cells in the bulge region and fibrosis of the affected area [10].

Diagnosis of alopecia due to radiation is typically based on clinical presentation (well-demarcated areas of alopecia localized to the areas of radiation treatment, typically without inflammation) and a history of exposure to radiation in the past month [2]. Dermoscopic findings at lower radiation doses are similar to those of alopecia areata, with yellow and black dots, short vellus hairs, broken hair, coiled hair, and white dots being common [6]. At higher doses associated with cicatricial alopecia, dermoscopy will show decreased hair density, white patches, and the absence of follicular openings [10].

Treatment

As alopecia can be such a concerning side effect of treatment, it is important to counsel patients on the potential timing of their hair loss and that most cases will spontaneously resolve. Additionally, management strategies do exist for radiotherapy alopecia. Some of these include preventative therapies, topical medications, injections, and surgery. The way the radiation treatment itself is delivered can also have an impact. To reduce off-target radiation and spare healthy hair, newer treatment planning strategies such as intensity modulated radiotherapy and volumetric-arc therapy (both of which employ linear accelerators and precision treatment planning to treat tumors while minimizing exposure of the scalp) can be employed [10]. Scalp cooling, which may have utility in some other conditions, has not been shown to be preventative for alopecia due to radiation [11].

Preventative therapies such as nitroxides or prostaglandin E2 prior to radiotherapy have been shown to be possibly preventative for alopecia [6]. Topical silymarin (an extract from milk thistle), subcutaneous amifostine, and oral pentoxifylline are other agents that have been studied for prevention [9]. All of these medications have antioxidant properties and are theorized to improve blood flow and inhibit fibroblast proliferation at the area of treatment. Cholecalciferol (vitamin D_3), which has some evidence for potentially regulating gene transcription and increasing the expression of keratins, appears to be preventative in some studies [12]. Less proven preventative therapies include the application of topical epinephrine or norepinephrine, which conferred up to 95% coat retention in a study of rats exposed to radiation [13].

Topical minoxidil 5% solution has been used for the treatment of persistent alopecia with moderate success. One study reported an 82% subjective response rate among patients with radiation-induced alopecia lasting longer than 6 months [10]. Minoxidil is thought to cause local vasodilation via ATP-dependent potassium channel activation, and stimulation of resting hair follicles into the anagen phase. A good response is typically achieved in 4 months with twice daily use but may take over a year if exposed to higher doses of radiation.

N-acetylcysteine, available in both topical and oral forms, is another potential therapy. Through its anti-inflammatory effects on IL-6, TNF-α, and IL-1, it is thought to reduce the cascade of cytokines that results from damaging radiation on epithelial cells [14]. By donating a cysteine and replenishing glutathione, n-acetylcysteine also exerts antioxidant effects. This reduces reactive oxygen species that could potentially damage cellular organelles.

Botulinum toxin type A injection has mixed evidence, with some case reports supporting its use to treat radiotherapy alopecia [15]. The theorized mechanism of this improvement was an increased blood flow to the tissues of the scalp, via relaxation of the musculature. One such report injected muscles around the scalp (including frontalis, temporalis, periauricular, and occipitalis muscles) at 30 injection sites every 3 months for 12 months. There was minimal effect noted at 3 months, with more modest increases in hair density and thickness noted after 12 months.

For cases of alopecia refractory to treatment, reconstructive surgical options may be considered. In pediatric patients, a variety of techniques have been reported with good success [16]. Choice of surgical technique should be guided by the pattern and location of hair loss, and include simple excision, scalp flap surgery, and tissue expansion. Transplantation can also be considered and has a success rate reported to be as high as 85% even in areas of poor vascularization. Some hair growth may be observed within 3 months after transplant, but full results are often not realized for over 1 year.

Key Points

- Alopecia due to radiation exposure follows a dose-response relationship, with transient anagen effluvium expected at doses above 2 Gy, and potential for permanent hair loss at doses above 43 Gy.

- Hair loss begins 1–3 weeks after radiation exposure and will resolve spontaneously in 2–6 months for low doses.
- As alopecia can be such a concerning side effect of treatment, it is important to counsel patients on the expected timing for appearance and resolution of this potential event.
- While no treatments have been found to be entirely effective, the use of preventative medications, topical agents, reconstructive surgery, and transplantation have all been tried with some success.

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70-Year-Old Male with a Slow Growing Painless Nodule on the Scalp

20

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Abstract

Alopecia neoplastica (AN) is a rare subtype of scarring alopecia that is caused by metastasis from underlying malignancies, most frequently from primary visceral tumors such as in breast tissue. AN presents more frequently in women but has a poorer prognosis when diagnosed in men. The clinical presentation of patients affected with AN consists of nodular red-violaceous lesions in the frontoparietal scalp with or without scaling. Although AN most commonly occurs after the diagnosis of the primary tumor, diagnosis of AN may be challenging especially if its onset occurs prior to the primary tumor diagnosis. The histological findings of AN consist of the metastatic carcinoma cells infiltrating into the dermis and subcutaneous tissue, fibrosis of the dermis and subcutaneous tissue, the loss of pilosebaceous units, and the pleomorphic cellular morphology that is typical of adenocarcinoma. The proposed mechanism of AN involves the release of cytokines from metastatic carcinoma cells leading to fibrosis and destruction of pilosebaceous units. The identification of skin metastases plays a role in staging and treatment of the disease, making it vital to identify them early. Treatment of AN is primarily focused on systemic treatment for the primary tumor. Although case reports of regrowth are present, patients should be counseled on the scarring nature of the hair loss as well as the generally poorer prognosis associated with AN.

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_20

Keywords

Alopecia neoplastica · Cutaneous metastasis · Metastatic carcinoma · D2–40 · Chemotherapy

A 70-year-old male presented with a nodule on the right temporal scalp. It was present for about 4 months. He had no significant health problems but was a smoker since age 17. He denied weight loss, fever, or chills. He reported mild fatigue, but he attributed it to working as a truck driver and having long hours lately.

On physical examination, a 1.5 cm subcutaneous fixed nodule was observed on the right temporal scalp. The hair was absent in that area. The remaining scalp exam was within normal limits. The eyebrows, eyelashes, and fingernails were normal on exam. A biopsy was performed and revealed a poorly differentiated carcinoma with variably sized dark blue nuclei within scant cytoplasm, molding, and crush artifact. Staining with synaptophysin and TTF-1 was positive and CD45 was negative.

Based on the clinical case description, what is the cause of his alopecia?

1. Renal cell carcinoma metastases
2. Small cell carcinoma of the lung metastases
3. Melanoma metastases
4. Lymphoma

Diagnosis

Small cell carcinoma of the lung.

Discussion

The prevalence of skin metastases (SM) ranges from 0.7% to 9% in patients with internal tumors, and the estimated rate of SM is approximately 5.3% [1]. Alopecia neoplastica (AN) is a rare form of cutaneous metastasis that accounts for 4% of all cases of cutaneous metastases and involves the spread of an underlying cancer to the scalp, with an overall incidence ranging from 0.7% to 0.9% [2]. Women are more frequently affected by AN than men, but men with AN have a worse prognosis. Metastases most commonly originate from primary visceral tumors, most of which are of breast tissue origin. Other sources of primary tumors for AN include gastrointestinal, cervical, and trophoblast tissue [3–5]. Rarely, desmoplastic melanoma, a subtype of melanoma characterized by atypical spindle-shaped melanocytes and abundant collagen deposition, can present as primary AN [6, 7]. Although AN most commonly occurs after the diagnosis of the primary tumor, diagnosis of AN may be challenging especially if its onset occurs prior to the primary tumor diagnosis [8]. In approximately 17% of AN cases, skin metastases may occur before or at the same

time as the detection of the primary cancer [7]. While skin metastases can help identify new primary tumors, they can also play an important role in the surveillance of cancers thought to be in remission. The identification of skin metastases plays a role in staging and treatment of the disease, making it vital to identify them early.

The clinical presentation of AN most frequently consists of a localized asymptomatic nodular scarring alopecia with red-violaceous or flesh-colored nodular lesions on the frontal or parietal region of the scalp. The erythematous appearance of AN lesions is explained by the fact that the scalp has a relatively high blood supply [8]. It is common for AN to present as single or multiple nontender nodules, and the affected area of the scalp is distinctly erythematous with or without scaling, sometimes covering a subcutaneous nodule or presenting with multiple overlying telangiectasias [2]. Severe itching has also been reported in some cases of AN, leading to the false diagnosis of eczema [2]. Furthermore, the diagnosis of AN can be justified by the persistence of hair loss in well-defined areas of the scalp after the secondary effects of chemotherapy have subsided [2].

Histologically, AN is characterized as an adenocarcinoma due to the relatively high density of glands in the scalp [8]. Histological examination also reveals metastatic carcinoma cells in a dense collagenous stroma infiltrating into the dermis and subcutaneous tissue, along with loss of pilosebaceous units [9]. The dermis is fibrotic, and metastatic cells are present in the reticular dermis or subcutaneous tissue [10]. The cells can also be found in a single-file configuration between layers of fibrotic collagen [10, 11]. Histologic characteristics of AN are consistent with findings commonly associated with cancerous tissue, such as nuclear atypia, pleomorphic and hyperchromatic spindle-shaped cells, and molecular profiles consistent with the primary tumor [2, 6]. Additional staining may be needed to determine the primary tumor pathology. For instance, AN from primary gastric adenocarcinomas may stain positively for MSH-2, and AN from primary breast cancer may stain positively for estrogen receptor, progesterone receptor, and CK7 [2, 10].

The mechanism of AN is not well known; however, it is likely that the fibrosis from the release of cytokines by metastatic carcinoma cells may cause the loss of hair follicles [10]. Additionally, tumor invasion and destruction of hair sheaths may be involved in the formation of areas of alopecia since hair can be regrown after the completion of effective cancer treatment [9]. Furthermore, cutaneous metastases to the scalp from primary breast cancer are mediated through lymphatic vessels, irrespective of the clinical features of the primary tumor, according to a 2011 study of the lymphatic-specific marker D2–40 [12].

Treatment

Treatment of AN most often involves systemic treatment of the primary tumor by chemotherapy. Surgical excision alone or in combination with radiotherapy or chemotherapy is used less commonly, and chemotherapy remains the most frequently reported method of treatment for AN [9]. Following successful treatment of the

primary tumor, it is possible to restore the hair follicles in non-scarring areas of alopecia that were formed due to chemotherapy-induced hair loss [2].

As the alopecia is caused by a cutaneous metastasis of a visceral malignancy, treatment is focused on the primary tumor pathology. With systemic treatment, the hope is that scalp metastases will regress, thus making hair regrowth possible. It is important to counsel patients on the scarring nature of the metastasis, and that systemic treatment of the cancer may result in further alopecia that is non-scarring in nature. Cosmetic remedies such as wigs may be an option based on patients' personal preferences. As this presentation of hair loss is generally a distant metastasis, staging will be advanced, suggesting a poorer prognosis, and patients should be counseled on this as well.

Although AN generally results in a scarring form of hair loss due to fibrosis, there have been case reports where regrowth was reported with systemic treatment. For instance, a case report of a patient with breast cancer and scalp metastasis illustrated that systemic treatment provided the possibility of hair regrowth [10]. Although there was progressive drug-induced alopecia due to tamoxifen treatment, the patient's scalp metastasis regressed at the end of the treatment course. Additionally, 2 years post-treatment, hair regrowth was evident. The regrowth was most likely possible due to non-fibrotic causes of the initial hair loss such as tumor invasion of the hair sheath [10]. Therefore, treatment of the underlying malignancy would result in regrowth in areas of alopecia.

Key Points

- Alopecia neoplastica often presents as erythematous nodular lesions and telangiectasias on the frontoparietal scalp and is associated with visceral tumors, most commonly originating in gastrointestinal or breast tissue.
- Systemic treatment targeted at the primary tumor is the mainstay of treatment for alopecia neoplastica.
- Despite the rarity of alopecia neoplastica, patients who present with new atypical areas of scalp alopecia should be thoroughly evaluated to ensure the hair loss is not due to cutaneous metastasis of a visceral malignancy.

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40-Year-Old Female with a Scaly, Gray Patch of Hair Loss on the Left Parietal Scalp

21

Cara Palusak, Kaitlyn Blacha, Suchita Sampath, and Shannon C. Trotter

Abstract

Tinea capitis is an infectious disease most commonly seen in the pediatric population affecting hair follicles of the head and scalp. The causative microbes are dermatophyte species capable of invading keratinized tissue of the hair. Although the prevalence of causative dermatophyte species differs based on geographical patterns and region of infection, the most common microbes are *Microsporum* and *Trichophyton* species. Symptoms of tinea capitis can vary widely including pruritus, scaling, inflammation, broken hairs, patchy alopecia, papules, and pustules. This range of presentation occurs based on the causative dermatophyte, type of hair follicle invasion, and host inflammatory response. The three types of hair follicle invasion are ectothrix, endothrix, and favus forms. The host inflammatory response is classified as non-inflammatory and inflammatory types, which are dependent on both host response to the infective dermatophyte and the propensity of the infective dermatophyte to cause inflammation in hosts. When diagnosing tinea capitis, the gold standard currently is mycological examination. Due to the high cost, invasiveness, and length of time, it takes to perform mycological examination, trichoscopy is a useful method to aid in diagnosis and monitoring of treatment while awaiting results. While performing trichoscopy, the presence of both broken or dystrophic hairs and perifollicular scale is more highly associated with positive mycological cultures than finding dystrophic hairs alone. In the treatment of tinea capitis, the highest cure rates were seen with

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_21

the use of griseofulvin or terbinafine. The choice in treatment often comes down to cost and local geographic patterns of infectivity. Additional topical treatments have been studied for use within the first 2–4 weeks to aid in reducing the transmission of tinea capitis to others.

Keywords

Tinea capitis · Alopecia · Dermatophyte · Griseofulvin · Terbinafine

A 40-year-old female presented with a gray, flakey, patch of hair loss on the left parietal scalp. She stated that it began around 4 months ago as a small scaly area and gradually expanded and the hair fell out. The area was very itchy at times, and she treated it with a topical corticosteroid solution with little improvement. She denied hair loss elsewhere. Her medical history was significant for multiple sclerosis and was currently on treatment.

On physical examination, there was a well-demarcated, white, scaly alopecic patch on the left parietal scalp (Fig. 21.1). The rest of the scalp was normal on exam. The eyebrows and eyelashes were of normal density and the fingernails were unremarkable. A Wood's lamp evaluation was positive for fluorescence.

Based on the clinical case description, what is the most likely diagnosis?

1. Seborrheic dermatitis
2. Discoid lupus erythematosus
3. Tinea capitis
4. Trichotillomania

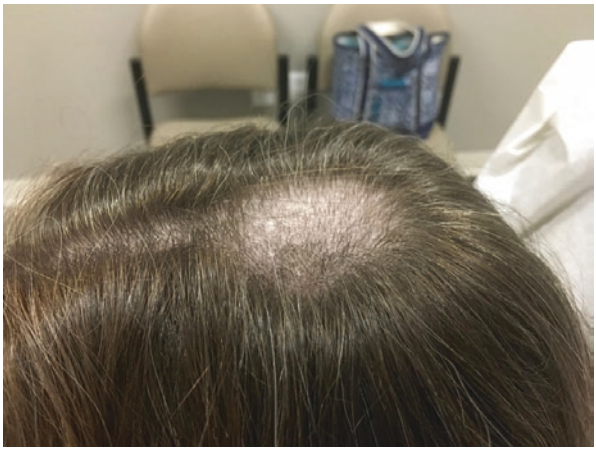

Fig. 21.1 Well-demarcated, white, scaly, patch of non-scarring alopecia and few sparse hairs on the left parietal scalp

Diagnosis

Tinea capitis.

Discussion

Tinea capitis is an infectious disease of the scalp and associated hair follicles caused by dermatophytes capable of infiltrating keratin-containing tissue [1]. It most commonly affects prepubescent children between the ages of 3–7 years old, but infants and adults can also be infected. The likelihood of infection in all age groups increases with comorbidities such as diabetes, anemia, prolonged steroid use, immunosuppression, or cancer. In addition, shorter hair is a risk factor due to the increased proximity of fungal colonization to the scalp [2]. The main causative agents are *Microsporum* and *Trichophyton* species, although *Epidermophyton* species are also noted. The only identified dermatophytes unable to cause tinea capitis are *Trichophyton concentricum* and *Epidermophyton floccosum* [2]. The prevalence of dermatophyte species differs based on the geographical region of infection. Over the past 20 years, there have been changing patterns of endemic organisms likely due to increased travel, immigration, emigration, and surveillance [1, 2]. Patterns currently demonstrate a global increase in dermatophyte diversity [3]. In the United States, *Trichophyton tonsurans* has risen in recent years and continues to be a challenge for infection control [4].

Common symptoms of tinea capitis include red papules on the scalp, circular patches with inflamed borders, itching, scaling, and diffuse or patchy alopecia; however, the clinical presentation can widely range from broken hairs with mild scaling to inflamed pustule formation with surrounding alopecia. Presentation differs based on the causative organism, type of hair invasion by the dermatophyte, and degree of inflammatory response by the host [1, 2].

The three general categories of hair invasion are ectothrix, endothrix, and favus types. The ectothrix form causes hair breakage 2–3 mm above the scalp with scaling and inflammation and is commonly caused by *Microsporum* species which illuminate under Wood's light. The endothrix form causes hair breakage down at the scalp resulting in swollen hair follicles (black dots) and is commonly caused by *Trichophyton* species which do not illuminate under Wood's light. The favus form causes air within the hair shaft resulting in longer, matted hair with yellow crusting around the shaft, and is caused by *Trichophyton schoeleinii* [2].

Tinea capitis is clinically classified as non-inflammatory and inflammatory types. Non-inflammatory types include generalized or patchy fine scaling with little alopecia resembling dandruff, single or multiple circular patches of scale with associated alopecia (gray patches), and patches of alopecia with scaling and speckled broken hair shafts at the scalp (black spots) [5]. Inflammatory types include pustular form,

favus, and kerion, which are more highly associated with the development of alopecia. The pustular form presents with pustules and patches of alopecia. Favus presents with cicatricial alopecia, yellow-crusting, and hair follicular erythema. Kerion, which may resemble bacterial abscesses, presents initially with dermatophyte folliculitis that progresses to erythema, pain, inflammation, crusty carbuncle-like plaques, and pustules. Dermatophytid reactions resulting from kerion classically present with the "ear sign," or scaling and erythematous papules located in the retroauricular, helix, and antihelix regions [2].

The gold standard for diagnosis of tinea capitis is mycological examination using fungal cultures and microscopy; however, the use of trichoscopy is a non-invasive, cost-effective method useful in diagnosing and monitoring therapy while waiting on culture results from mycological testing or when it is not available [6]. When diagnosing tinea capitis, it is important to differentiate it from other possible diagnoses such as alopecia areata, seborrheic dermatitis, discoid lupus erythematosus, bacterial abscess, and trichotillomania [1]. Common findings on trichoscopy include perifollicular scaling, broken hairs, black dots, comma hairs, corkscrew hairs, morse-code-like hairs, zigzag hairs, bent hairs, and block hairs [6]. In diagnosing tinea capitis on trichoscopy, the presence of both perifollicular scale and broken or dystrophic hairs is more highly correlated with positive cultures than dystrophic hairs alone [7]. When analyzing the types of dystrophic hairs, comma hairs and corkscrew hairs remain specific markers of tinea capitis, as they are often seen together and resolve upon treatment [8]. In addition, corkscrew hairs are more common with infection by *Trichophyton* species although they can be seen in *Microsporum* species, and only infection with *Microsporum* species exhibited morse code-like hairs, zigzag hairs, and bent hairs [6]. Yet, more studies need to be done to confirm these findings, as not all sources demonstrate a correlation between trichoscopy findings and the type of dermatophyte [8]. Lastly, the use of Wood's light examination to initially identify the organism as a dermatophyte yields little benefit in western countries, as *Trichophyton tonsurans* is most prevalent and does not fluoresce [4]. The more recent advent of real-time polymerase chain reaction testing for detection may be of use, but consideration of the cost of equipment, time spent preparing samples, and importance of result speed must be weighed against using current methods [9].

Treatment

The mainstay of treatment for tinea capitis is systemic antifungal medication, as topical antifungals alone have high rates of relapse and do not fully penetrate the hair shaft [10]. The two most common first-line treatments are griseofulvin and terbinafine. Griseofulvin is historically the treatment of choice due to its low cost and high accessibility [11]. In a systematic review of management for tinea capitis, both griseofulvin and terbinafine demonstrated the highest cure rates resulting in both negative mycological testing and relief of clinical symptoms. Griseofulvin is effective for the treatment of *Microsporum* species and often must be used as prolonged treatment for *Trichophyton* infections. It has fungistatic properties and faster

elimination from the body, so it must be given for a longer period of time than terbinafine [4]. In recent years, there has been a decrease in the efficacy of griseofulvin likely due to changes in geographical dermatophyte profiles, genetic mutations, and poor compliance with the duration of therapy resulting in lower susceptibility [11].

Gupta et al. (2018) reported that terbinafine has comparable results with griseofulvin when treating tinea capitis caused by *Trichophyton* species; however, it must be administered for a longer period when treating *Microsporum* infections [11]. It has a higher affinity for keratin-containing tissues resulting in decreased length of treatment but has a greater amount of biodistribution that may result in increased adverse reactions [4].

Since approximately 95% of cases of tinea capitis in the US are caused by *Trichophyton* infections, the use of terbinafine as a first-line medication is justified. When the causative dermatophyte is unclear or kerion is present, griseofulvin is the preferred treatment. If the kerion is not treated with griseofulvin, the risk of permanent scarring and alopecia increases [10]. Performing an adequate history to determine risk factors and exposures, understanding the geographical dermatophyte profile, and using trichoscopy findings can help to direct which treatment to choose.

Other treatment regimens including oral itraconazole, ketoconazole, and fluconazole have also been studied, but are inferior to griseofulvin and terbinafine [4]. Topical adjunctive treatment with selenium sulfide, ketoconazole, or ciclopirox shampoos can also be used for the first 2–4 weeks or until mycological cure, as they may aid in reducing transmission [10].

Key Points

- Tinea capitis is a dermatophyte infection of the scalp and associated hair follicles common within the pediatric population.
- Common causes of tinea capitis include *Trichophyton* and *Microsporum* species, while the specific infectious pathogen highly depends on the geographical region of infection.
- Tinea capitis exhibits a wide range of clinical presentations from patchy, fine scaling to erythematous pustules and alopecia.
- The gold standard for diagnosis of tinea capitis is mycological testing; however, a cost-effective and accessible method for diagnosis and treatment monitoring while waiting for mycological results is trichoscopy.
- Griseofulvin and terbinafine are considered first-line treatments for tinea capitis.

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38-Year-Old Female with Patchy Alopecia Diffusely on the Scalp, Headache, Fatigue, and Rash

22

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Abstract

Syphilis is the most rapidly increasing sexually transmitted disease in the United States. Of those patients who develop secondary syphilis, only about 8% will develop alopecia. Even so, with a rise in case numbers, there will be a concurrent rise in the number of patients presenting with syphilitic alopecia. Alopecia due to syphilis frequently presents as a moth-eaten pattern diffusely across the cranium; however, it has been dubbed the great mimicker due to its presentation taking many forms and copying other causes of alopecia. The pathophysiology behind syphilitic alopecia is thought to be due to a vasculitis in the peribulbar vessels leading to a lymphocytic infiltration and ultimately hair loss. While it is difficult to differentiate from other causes of alopecia, taking a thorough history can help narrow the differential by asking about sexual activity, other known syphilis symptoms, and looking for systemic effects. Infection is generally screened for with Rapid Plasma Reagin (RPR) test and positive screens confirmed using a treponemal test such as Treponema Pallidum Particle Agglutination (TPPA), Fluorescent Treponemal Antibody Absorption test (FTA-ABS) or even Polymerase Chain Reaction (PCR) Currently the best form of treatment is treating the underlying syphilitic infection. Penicillin G 2.4×10^{66} units IM as a

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_22

one-time dose remains the mainstay treatment of choice. Symptoms of alopecia resolve after successful treatment, typically within 3 months of infection resolution.

Keywords

Syphilis · Treponema pallidum · Syphilis · Alopecia · Rapid plasma reagin test · Penicillin g

A 38-year-old female presented with diffuse hair loss on her scalp, present for about 1 month. She also reported a rash on her face and body that started a few weeks ago. Some of the lesions are scaly and mildly itchy at times. She has tried a topical steroid cream with no improvement. In addition, she admitted to headaches, arthralgias, and fatigue. She reported feeling like she's had a flu-like illness over the past week.

On physical examination, there were several ill-defined patches of alopecia across the scalp. The eyebrows and eyelashes were of normal density. Her fingernails were normal. She also had diffuse scaly papules and patches on the trunk and face.

What screening test below is likely to diagnose the underlying condition most responsible for her hair loss?

1. HIV
2. RPR
3. CBC
4. TSH

Answer

RPR.

Discussion

Syphilis, caused by the spirochete bacterium treponema pallidum, is the most rapidly increasing sexually transmitted disease in the United States since 2015 with an increase of 74% in infection rate and an increase of 279% in congenital cases [1]. The demographics most impacted by this recent rise are premenopausal women, unborn children, and men who have sex with men (MSM) [2]. Infection is acquired through sexual contact of active lesions, mucous patches, and skin rashes, or through nonsexual sources such as in utero, blood transfusion, and organ transplant from infected patients [3]. *T. pallidum* rapidly invades microabrasions and mucous membranes traveling to the lymph and ultimately the blood within hours of contact [3].

The spirochetes then rapidly replicate and induce a local inflammatory response in infected tissues resulting in symptomatic presentation [4]. The clinical course is separated into four distinct stages: primary, secondary, latent, or tertiary infection. Each stage has distinct symptoms as well as different courses of treatment.

Early-stage or primary syphilis presents within 10–90 days of exposure most commonly at day 21 [1]. It is marked with a genital chancre; a solitary painless papule that erodes and becomes a hardened ulcer [3]. Resolution of the chancre is common with potential persistent lymphedema [3]. Secondary syphilis is marked by more systemic manifestations around 2–6 weeks post-infection. Common symptoms include a maculopapular rash involving the palms and soles of feet, condylomata lata, general malaise, fatigue, fevers, and alopecia [5]. After the resolution of secondary syphilis, patients either enter latent syphilis or progress to tertiary syphilis. Patients can remain latent and go undetected for 1–46 years; during this stage, they are considered non-infectious but can relapse into secondary syphilis or continue to tertiary syphilis [5]. Tertiary syphilis is marked by various systemic effects; most notably gummas, cardiovascular, and central nervous system involvement [5].

Alopecia due to syphilis is seen in 2.9%–7% of patients with secondary syphilis; however, this is likely an underreported statistic due to a subtle presentation [5, 6]. The non-scarring alopecia can have a pattern that mimics other forms of alopecia (e.g., areata) or can be diffuse, moth-eaten, or a combination of the latter two patterns [7, 8]. Additionally, the hair loss frequently has a predilection for the occipital and parietal regions of the scalp [9]. The mechanism of syphilis causing alopecia is thought to be related to vasculitis of the peribulbar capillaries of the hair follicle, leading to a lymphocytic infiltration with plasma cells preventing hair cycle progression and thus halting growth [10]. While it is difficult to differentiate from other causes of alopecia, taking a thorough history can help narrow the differential by asking about sexual activity, other known syphilis symptoms, and looking for systemic effects [7]. Regardless, physicians should maintain suspicion of syphilitic alopecia in any patient who is currently sexually active and presents with alopecia. Infection is generally screened for with nontreponemal tests such as the Rapid Plasma Reagin (RPR) test. After a positive screen, or if there is continued high suspicion of syphilis, the result is then confirmed using a treponemal test such as Treponema Pallidum Particle Agglutination (TPPA), Fluorescent Treponemal Antibody Absorption test (FTA-ABS) or even Polymerase Chain Reaction (PCR) [11]. Biopsy of the alopecic areas is generally not necessary but if performed, will show a reduction in the number of hair follicles, empty follicles, as well as dilated and tortuous vessels with capillary loss [6].

Treatments

Alopecia due to syphilis is treated by treating the underlying infection; hair regrowth normally occurs around 3 months after treatment [7]. The patient should be treated according to the stage and duration of syphilis infection. Patients experiencing primary, secondary, and early latent disease should be treated with benzathine

penicillin G 2.4 × 10^6 units IM one time [5]. Due to the long generation time of T. pallidum, 30–33 h, long-acting penicillins such as benzathine penicillin G is the preferred therapy to ensure full coverage of infection [4]. If the patient is allergic to penicillin, they may be alternatively treated with doxycycline 100 mg orally twice daily for 14 days or ceftriaxone 1–2 g daily either IM or IV for 10–14 days [12]. Special considerations should be made for pregnant women with a penicillin allergy who should be desensitized and administered penicillin due to teratogenic risks of doxycycline [5]. If a patient is experiencing late latent or tertiary syphilis, treatment should consist of benzathine penicillin G 2.4 × 10^6 units IM weekly for 3 weeks with the exception of neurosyphilis which requires hospital admission, and IV penicillin G 3–4 × 10^6 units every 4 h for 10–14 days [12]. Like patients who are pregnant, if a patient with neurosyphilis presents with a penicillin allergy they should be desensitized and utilize penicillin.

Key Points

- The number of syphilis cases in the U.S. is rapidly increasing; this suggests physicians will be seeing an increase in patients presenting with syphilitic alopecia.
- Alopecia due to syphilis can present in various forms that mimic other causes of alopecia but suspicion should always be raised with patients presenting with hair loss, particularly with a moth-eaten pattern.
- The mainstay treatment for syphilitic alopecia is to treat the underlying infection with penicillin and hair regrowth is expected within 3 months post-treatment.

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71-Year-Old Female with a Tender, Geometric, Scarring Patch of Alopecia on the Right Temporal and Parietal Scalp Associated with Headaches and Vision Changes

23

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Abstract

Giant cell arteritis (GCA), also known as temporal arteritis, is a non-necrotizing granulomatous vasculitis affecting medium- and large-sized arteries. It is the most common vasculitis in North America and Europe and primarily affects patients over the age of 50, with incidence increasing with age. Symptoms of GCA include headache, vision loss, jaw claudication, polymyalgia rheumatica, and occasionally scalp necrosis with alopecia. Several long-term disease processes associated with GCA include hypertension, osteoporosis, diabetes mellitus, and cataracts. The gold standard for diagnosis of GCA is with temporal artery biopsy. Other imaging modalities such as ultrasound, CT scan, MRI, and [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan can aid in the diagnosis of GCA. Non-specific inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may be elevated as well. If GCA is suspected, glucocorticoids are the first-line treatment and should be started immediately. Initiation of glucocorticoid therapy prior to confirmatory biopsy is imperative to prevent vision loss. Glucocorticoids are associated with many side effects such as cushingoid appearance, weight gain, and hyperglycemia but remain first-line treatment due to their efficacy. Several other medications have been studied as adjunctive therapy to glucocorticoids in the treatment of GCA. These medications include methotrexate; tocilizumab

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S. C. Trotter, S. Sampath (eds.), *Clinical Cases in Alopecia*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-031-15820-9_23

(TCZ), an IL-6 antibody; abatacept, a CTLA-4 antibody, and ustekinumab, a monoclonal antibody that targets IL-12 and IL-23. Adjunctive therapy has been shown to decrease the overall dose of glucocorticoid therapy and to maintain disease relapse after initial treatment.

Keywords

Temporal arteritis · Giant cell arteritis · GCA · Scalp necrosis · Glucocorticoid · Polymyalgia rheumatica · Scarring alopecia

A 71-year-old female presented with a sudden onset of hair loss on the right scalp. The patient stated that it began a few months ago, along with headaches and changes in vision. She reported a personal history of thyroid disease, dry eyes, dry mouth, and multiple blood clots. Of note, her family history was significant for lupus. She denied any rashes on her body or sun sensitivity. She also denied any new joint pain but admitted to muscle soreness. She was not currently on any treatment. Previously, she was evaluated by a rheumatologist. Her work up for systemic lupus was negative but was suggestive of polymyalgia rheumatica.

On physical examination, there was a tender, boggy, geometric patch of scarring hair loss on the right temporal scalp, extending to the right parietal scalp. A scalp biopsy was performed and revealed scarring alopecia with compact orthokeratosis with follicular plugging with dermal fibrosis and perifollicular lichenoid inflammation.

What test below is not a part of the typical diagnostic work up for the underlying condition most responsible for her hair loss?

1. Erythrocyte sedimentation rate (ESR)
2. High-resolution MRI
3. Temporal scalp biopsy
4. RPR

Answer

RPR.

Discussion

Giant cell arteritis (GCA), also known as temporal arteritis, is a non-necrotizing, granulomatous vasculitis that affects medium and large-sized arteries [1]. The most common arteries involved are the temporal artery and its branches, leading to symptoms such as headache, vision loss, jaw claudication, polymyalgia

rheumatica (PMR), and scalp necrosis, which can lead to subsequent alopecia. Scalp necrosis is a rare complication of GCA but is associated with increased disease severity [2]. The overall clinical presentation of GCA often varies between patients, indicating a high degree of clinical suspicion to properly diagnose and treat the condition.

GCA is the most common vasculitis in North America and Europe and often affects patients over the age of 50 [3]. The incidence of GCA increases with age. Inflammatory infiltrates form multinucleated giant cells between the arterial intima and the media, which subsequently disturb the internal lamina and can lead to ischemic changes [1]. The inflammatory nature of the condition can manifest in nonspecific ways including fever, malaise, anemia, and constitutional symptoms. More specific symptoms can include headache, irreversible vision loss, and jaw claudication, along with PMR, which can occur before or after the other symptoms of GCA [1]. Vision loss and blindness can occur due to the occlusion of the ophthalmic artery, a branch of the temporal artery, even after the onset of treatment [4, 5]. Complete infarction of an artery is less common but can occur, leading to strokes or affecting regions such as the scalp, tongue, or extremities [1]. Scalp necrosis typically presents with crusting in the hair in a temporoparietal distribution that can lead to scarring alopecia in addition to other symptoms of GCA [4, 6]. Dermatologic manifestations of GCA are rare but can also include edema, urticaria, vesicles, erythema, and purpura in the distribution of the occluded artery [4].

Newly diagnosed GCA is associated with numerous new-onset comorbidities such as hypertension (55.4%), osteoporosis (18.3%), diabetes mellitus (Type 1 or 2) (14.2%), and cataracts (13.9%) [5]. As a result, patients should be monitored for relapse and new co-morbid conditions years after a GCA diagnosis.

Although a temporal artery biopsy is the gold standard of diagnosis for GCA, its low sensitivity compels practitioners to begin treatment even before obtaining the biopsy [5, 7]. Histopathology reveals transmural blood vessel inflammation containing CD4+ T-cells, T_H1 cells, T_H17 cells, T_{regs} cells, macrophages, inflammatory infiltrates, and multinucleated giant cells [5]. A temporal artery biopsy sample should be at a minimum 1 cm in length to ensure an adequate sample size [7].

Imaging modalities may also be utilized in the diagnosis of GCA. Ultrasound, CT scan, MRI, and [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan have shown to aid in the diagnosis of GCA with or without a temporal artery biopsy [8]. Non-specific inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly elevated. A combination of biopsy, imaging studies, inflammatory markers, and clinical presentation is the definitive way to diagnose GCA [8]. Several investigations including chest radiography, echocardiography, DEXA scans, CBC, and acute phase reactant levels should be monitored to assess for disease relapse [9]. Follow-up visits should be scheduled regularly for the first six weeks after diagnosis and in intervals of 3 months until a year has passed since diagnosis.

Treatment

Glucocorticoids are the first-line treatment for patients presenting with GCA and should be initiated prior to obtaining a biopsy to mitigate the risk of blindness [1]. In the presence of inconclusive biopsy or imaging studies, glucocorticoids should be continued if GCA is suspected clinically [7]. Initial therapy, in the setting of vision loss, starts with 0.5–1 mg of IV methylprednisolone for 3 days before starting oral glucocorticoid therapy [9]. After initial IV methylprednisolone therapy, or in cases of uncomplicated GCA, starting doses of 40–60 mg of oral prednisolone for at least 3–4 weeks are prescribed to protect the contralateral eye from vision loss, and to help rapidly reduce the symptoms associated with GCA [9]. Patients with scalp necrosis and hair loss should be counseled on the permanent nature of their alopecia but that further hair loss can usually be avoided with proper management; glucocorticoids may lessen the severity of secondary cicatricial alopecia and scalp necrosis associated with GCA [10]. Tapering from the initial glucocorticoid dose should take place slowly over 1–2 years to help prevent relapse [9]. The suggested tapering regimen includes tapering 10 mg every 1–2 weeks until a 20 mg dose is achieved, then by 2.5 mg every 1–2 weeks until a dose of 10 mg is achieved and lastly tapering by 1–2 mg every 1–2 months until there is evidence of remission [9]. One meta-analysis found that increased duration glucocorticoid therapy was associated with decreased incidence of major relapse [11]. The most common manifestations of relapse included jaw claudication (44.3%), ophthalmological disturbances (32.7%), peripheral limb ischemia (12.5%), and involvement of the aorta (7.7%) [11]. Long-term glucocorticoid therapy is associated with side effects such as cushingoid appearance, hyperglycemia, osteoporosis, neuropsychiatric changes, and adrenal insufficiency. Despite the side effects associated with glucocorticoids, they remain the first-line treatment for GCA due to their efficacy.

Considering the side effects associated with long-term doses of prednisone, trials have investigated using immunosuppressive agents as adjuncts. These trials for drugs like methotrexate, tocilizumab, abatacept, and ustekinumab have all shown superior treatment efficacy, decreased dose of cumulative prednisone used, and decreased rates of GCA relapse when compared to prednisone monotherapy [12–16]. Methotrexate inhibits the folic acid cycle and should be considered in cases when there is recurrent GCA relapse or during a prolonged taper from glucocorticoids [9]. An effective dosage of methotrexate adjunctive therapy is between 7.5–15 mg per week. Side effects associated with methotrexate include macrocytic, megaloblastic anemia, elevated liver enzymes, and increased risk of infection. Tocilizumab (TCZ) is a monoclonal interleukin 6 (IL-6) antibody that targets the IL-6 receptor. IL-6 is a proinflammatory cytokine and acute phase reactant that results in Th17 cell differentiation and is involved in the pathogenesis of GCA [17]. Clinical GCA improvement in patients receiving tocilizumab adjunctive therapy can be visualized on both ultrasound and FDG-PET/CT imaging studies [18]. Tocilizumab is relatively safe, with an increased infection rate being the most common side effect. However, less common side effects associated with TCZ include neutropenia, stroke, liver toxicity, and cardiovascular complications [13, 19]. One

trial showed improved quality of life (QoL) measures associated with tocilizumab adjunctive therapy compared to prednisone monotherapy [18]. Abatacept is a CTLA-4 antibody that binds the CD-80/86 receptor and acts as a negative regulator of T-cell activation and co-stimulation [20]. The binding of D-80/86 prevents activation of the T-cell CD28 receptor, in turn, preventing CD4+ T-cell activation and IL-6 production [21]. Abatacept was also associated with few side effects, the most common being infection, along with three cases of malignancy being reported as well [20]. Ustekinumab is a monoclonal antibody that targets IL-12 and IL-23, disrupting the immune response mediated by Th17 and Th1 cells, which are key mediators in GCA pathogenesis [16, 21]. The most common side effects associated with ustekinumab include minor infections, alopecia, and non-dermatomal limb paresthesia [16]. Overall, numerous promising adjunct medications have been shown to be both safe and efficacious in the treatment of GCA (Fig. 23.1).

Patients should be provided with information about surgical treatments for their scarring alopecia once the disease is no longer active. Surgical options include transferring healthy parieto-occipital flaps, skin grafting, excising affected tissues, and tissue expansion of adjacent hair-bearing areas [22]. Treatment modalities are patient-specific and determined based on the location, size, and shape of the affected areas. Hair-bearing scalp flaps are used when the defect is too large for other surgical procedures, and they provide superior aesthetic results to grafts and require shorter healing times [23]. However, the downside to flaps is that they leave long

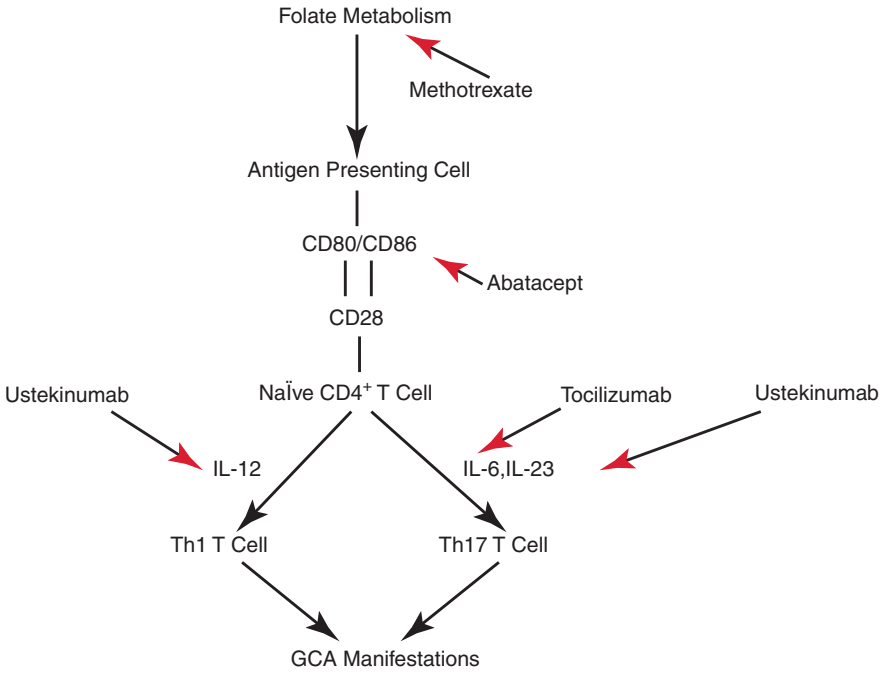

Fig. 23.1 Mechanism of action for adjunctive therapies used to treat GCA

scars, a defect at the donor site that equals the size of the flap, and decreased flap sensation [24]. Scalp reduction may be effective for reducing some or all the alopecic areas over the vertex scalp [25]. Tissue expansion can be used in large defects and has the benefit of recruiting tissue that is both sensate and hair-bearing, producing excellent results; however, its high complication rate of 60%, cost, and need for multiple procedural steps can make it a nonideal option for patients. As a result, this technique should only be used as an adjunct along with other reconstructive procedures [22].

Key Points

- Giant Cell Arteritis (GCA) is a non-necrotizing, granulomatous vasculitis that affects medium- and large-sized vessels.
- Gold-standard diagnosis of GCA is via temporal artery biopsy but imaging modalities such as ultrasound, CT scan, MRI, and PET scan can be utilized in the diagnosis of GCA.
- GCA is associated with causing several comorbid conditions such as hypertension, osteoporosis, diabetes mellitus, and cataracts but the most serious side effect is vision loss due to occlusion of the ophthalmic artery.
- Glucocorticoids are the gold standard in the treatment of GCA and should be initiated before the diagnosis can be confirmed.
- Several immunosuppressive medications have shown efficacy as adjunctive therapy to glucocorticoids in treating GCA including methotrexate, tocilizumab, abatacept, and ustekinumab.

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