Chapter 5

Cicatricial Alopecia

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Additional information is available at the end of the chapter

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Abstract

Cicatricial alopecia represents a group of disorders sharing a final pathway of destruction followed by replacement with fibrous tissue of the hair follicle unit. Cicatricial alopecia is classified into two categories, namely primary cicatricial alopecia, in which the hair follicle is the sole target of a progressive inflammatory process in a group of diverse skin or systemic diseases, and secondary cicatricial alopecia, referring to the hair follicle destruction as a result of a nonspecific disruption of the dermis. Permanent hair loss may also occur in the late phases of some nonscarring alopecias that are called "biphasic alopecias." Based on the pathological characteristics, the lesions of primary cicatricial alopecia are divided into lymphocyte-predominant subgroup, neutrophil-predominant subgroup, or mixed subgroup. In principle, the primary goal of the treatment aims to attenuate the progression of the inflammatory and the scarring processes at the earliest phase of the disease. In clinical practice, the lymphocyte-predominant lesions are treated with immunosuppressive agents, whereas the neutrophil-predominant lesions are treated with antimicrobials or dapsone. As the efficacy of medication treatment against the cicatricial alopecia varies significantly, autologous hair transplantation is recommended to patients who have a relatively stable primary or a secondary cicatricial alopecia.

Keywords: cicatricial alopecia, hair follicle unit, inflammatory progression, hair transplantation, follicular unit extraction

1. Introduction

Alopecia, also known as baldness or hair loss, refers to the partial or complete loss of hair over the body, although the hair loss over the head may be the most concerned issue among a large number of people who pursue medical assistance. Hair loss often causes the most

severe psychological distress in both sexes at the onset of symptoms and negatively affects self-image and self-esteem of the patient. The mechanisms underlying the alopecia are not fully understood, but the pathological progression results in the disintegration of the follicular unit and a permanent loss of ability to produce hair fiber [1]. In contrast to androgenic hair loss, the most common cause of alopecia, cicatricial (scarring) alopecia represents a group of disorders in which the common final pathway is the destruction followed by the replacement with fibrous tissue of the hair follicle unit [2]. Cicatricial alopecia leads to permanent damage of the stem cells in the hair follicle bulge; therefore, the end result is usually a permanent or irreversible loss of hair leaving the effacement of follicular orifices, the replacement of follicles with fibrotic stelae, and the fibrosis or hyalinization of surrounding collagen in the bald skin. The causes of cicatricial alopecia are categorized as primary or secondary [3]. In primary cicatricial alopecia, the follicle unit is the sole target during the pathological progression of the disease. In secondary cicatricial alopecia, the hair follicle destruction occurs as a result of a nonspecific disruption of the dermis, as in the thermal burns or blistering disorders. Permanent hair loss may also occur in the late phases of some nonscarring alopecias that are called "biphasic alopecias."

Pathologically, the causes of primary cicatricial alopecias are a diverse group of diseases that share common characteristics of skin inflammation. It is noted that the inflammatory processes confine within the scope of the hair follicular units although the cellular or molecular mechanisms involved are currently ill defined. Primary cicatricial alopecias should be considered as a trichologic emergency because this disease will progress to permanent hair loss if the management of the inflammatory processes is delayed [4]. Nevertheless, the treatment options are poorly defined and often limited in effect [2]. The secondary cicatricial alopecias can be caused by various cutaneous inflammatory processes or by physical trauma, which damages the skin and skin appendages.

Cicatricial forms of alopecia account for about 3.2% [5] of all trichologic consultations and the frequency of cicatricial alopecia is about 5.0–7.3% of all the hair loss cases [2]. The majority of affected European adults were females (female:male ratio = 2.6:1), and the primary cicatricial alopecia is more common than the secondary (primary:secondary cicatricial alopecia ratio = 4:1) [5]. A survey also reported that the prevalence of primary cicatricial alopecias is higher in women than in men in regions of Middle East, and the possible associating factors include social culture, scarf wearing, and treatment delay. Among the diseases that may cause primary cicatricial alopecia, pseudopelade of Brocq (PPB) (40.6%) was the most frequent one followed by lichen planopilaris (LPP) (12.6%), and folliculitis decalvans (FD) (11.2%). In another report, however, discoid lupus erythematosus (DLE) (33.9%) was the most common cause followed by pseudopelade of Brocq (PPB) (24.1%) and lichen planopilaris (LPP) (22.3%) [6, 7]. Histopathologically, the majority cases of primary cicatricial alopecia are characterized by lymphocytic infiltrate.

The efficacy of the treatments for various forms of cicatricial alopecia depends on the clinical diagnosis that requires quality inspection of individuals during the physical exam and laboratory tests. The following items are routinely utilized by many clinics:

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Physical exam

A. Gross inspection of hair: (a) generalized, patterned, or focal hair loss and (b) density of hair, presence of broken hairs, vellus (thin, downy premature hair) vs. terminal hairs (thick, strong mature hair).

B. Inspection of scalp: (a) absence of follicular ostia and scar tissue and (b) papules, pustules, scaling, and perifollicular erythema.

C. Diagnostic procedures: (a) hair pull test: useful for telogen effluvium; performed by grasping a small portion of hair and gently applying traction while sliding the fingers along the hair shafts. Evaluation of results: normal: 1–2 hairs removed; abnormal: ≥6 hairs removed; (b) direct microscopic inspections of hair shaft: exclamation point hairs: distal end broader than proximal end; seen in alopecia areata. Evaluation of the results: anagen hairs: elongated, distorted bulb with attached outer root sheath; telogen hair: club-shaped bulb; (c) "Hair growth window": repeatedly (weekly) shaving a small area of involved scalp to demonstrate normal regrowth; and (d) scalp biopsy: useful for the diagnosis of scarring alopecias [8].

Laboratory tests

Total and free testosterone and dehydroepiandrosterone sulfate serum concentrations. This test is useful for diagnosis and differential diagnosis of androgenetic alopecia.

Evaluation on tissue biopsy

Two skin biopsies each with more than 4 mm in diameter are required. The biopsy punch should be aligned with the hair shaft angle and should reach the deep subcutis when performing tissue punch. Under a microscope, the density and ratio of each type of the infiltrating inflammatory cells need to be recorded. In addition, some special staining of tissue sections is required that usually including staining of elastic tissue, Gram stain, periodic acid-Schiff stain, and colloidal iron stain for mucin. Tissue cultures or immunofluorescence studies are often required as well [9].

Principle of treatment

Spontaneous regrowth of hair in case of cicatricial alopecia hardly ever occurs. The primary goal of the treatment aims to attenuation of the progression of the inflammatory and the scarring processes at the earliest phase of the disease. The monitoring of disease activity by frequent clinical evaluation in combination with dermatoscopy observation should be scheduled. A practical way to assess the treatment responses is the evaluation through dermatoscopy. Bear in mind however, there is so far no clear consensus regarding the successful treatments in terms of their efficacy to cure cicatricial alopecia, and the clinical improvement on many subtypes of the disease has not been fully supported by evidence-based trials. Therefore, the treatment of cicatricial alopecias is selected in the absence of precise information on the expected outcome and the current treatment failure is common.

As a general rule, lymphocyte-predominant subgroup of primary cicatricial alopecias is treated with immunosuppressive agents. Neutrophil-predominant subgroup of primer cicatricial alopecias is treated with antimicrobials or dapsone. Systemic therapy is usually combined with topical or intralesional corticosteroids or topical calcineurin inhibitors. Adding anti-inflammatory shampoos is often recommended. The treatment effects may take 6 months or more to appreciate, and disease may resume upon discontinuation of systemic and/or topical therapy. The effectiveness of maintenance therapy is still elusive [2, 10].

Surgical treatment of stable cicatricial alopecia includes hair transplantations, excision of affected area, flap surgery, or scar reduction with tissue expansion.

2. Pathology of cicatricial alopecia

Although cicatricial alopecia includes a group of diverse diseases, there are currently several pathological features that are shared among some of the different subtypes of hair loss of this category. Understanding of such pathology traits would help understand the treatment strategies. From the clinical points of view, the pathological pathways of primary cicatricial alopecias merge into a few inflammatory processes that eventually result in the disintegration of hair follicular units. By consensus, four main categories are proposed based on the types of immune cell infiltrates during the pathogenesis of primary cicatricial alopecia (**Table 1**) [4].

Lymphocytic cicatricial alopecia
Chronic cutaneous lupus erythematosus
Lichen planopilaris (LPP)
Classic LPP
Frontal fibrosing alopecia
Graham-Little syndrome
Classic pseudopelade (Brocq)
Central centrifugal cicatricial alopecia
Alopecia mucinosa
Keratosis follicularis spinulosa decalvans
Neutrophilic cicatricial alopecia
Folliculitis decalvans
Dissecting cellulitis/folliculitis (perifolliculitis abscedens et suffodiens)
Keratosis follicularis spinulosa decalvans (KFSD)
Mixed cicatricial alopecia
Folliculitis (acne) keloidalis
Folliculitis (acne) necrotica
Erosive pustular dermatosis
Nonspecific cicatricial alopecia
Sebaceous gland abnormalities (primary or secondary)

Table 1. Immune cell infiltrates and their corresponding clinical diseases.

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Several lines of evidences in basic and clinical research have indicated that the local inflammatory destruction of the pilosebaceous unit leads to the permanent damage of the follicular stem cells in the bulge region and several associated hypotheses are suggested as following [1]: Autoimmune-mediated hypothesis: The autoantigens/epitopes that could elicit the autoimmune response are formed in the permanent region of the follicle including the stem cells in the bulge area; (2) immune privilege breakdown and Langerhans cell distribution hypothesis: MHC class I, β2-microglobulin, and MHC class II immune reactivity are significantly upregulated in the bulge region, and this reaction may be triggered by aberrant distribution of Langerhans cells; (3) bulge stem cell destruction hypothesis: The lost of Ck15 positive bulge stem cells is one of the evident histopathological traits of primary cicatricial alopecia; (4) hair Follicle Epithelial-Mesenchymal Communication Inhibition Hypothesis: As the induction of life-long cyclic transformations of hair follicles is epithelial-mesenchymal interaction dependent, inflammatory interruption in the communication between the epithelial stem cells and the hair follicle mesenchyme would damage the integrity of hair follicles [2]. (5) Peroxisome proliferator-activated receptor-γ (PPAR-γ) deletion hypothesis [2]: PPAR-γ, which is highly expressed in human sebaceous glands, plays roles in lipid homeostasis, sebocyte maturation, peroxisome biogenesis and anti-inflammatory effects. Dysfunction of PPAR-γ is believed to result in follicular inflammation and the pathogenesis of the primary cicatricial alopecia [11]; (6) Sebaceous Gland Dysfunction Hypothesis: The aberrant gene expressions in sebaceous gland lead to the abnormalities in the sebum secretion and hair growth; (7) "No Danger" Signal CD200 Deletion Hypothesis: In this hypothesis, the interruption of the ligand-binding signal between CD200 and its receptor is speculated as the trigger of local inflammatory reactions [12]; (8) Genetic Mutation of Keratin Hypothesis [2]: keratin gene mutation that associated with pathogenesis of alopecia microacanthosis leads to the disintegration of hair follicles.

As for secondary cicatricial alopecia, **Table 2** lists the lesions commonly seen in clinics that eventually result in reversible or irreversible hair loss.

Infection
Fungal (tinea capitis)
Bacterial
Viral (e.g., herpes zoster)
Immunologic
Sarcoidosis
Necrobiosis lipoidica
Morphea
Graft-versus-host disease
Malignancies
Alopecia neoplastica
Lymphoproliferative
Exogenous factors
Radiation
Burns
Drugs

Dermatoses
Psoriasis
Bullous disorders
Cicatricial pemphigoid
Epidermolysis bullosa
Hamartomas
Organoid nevus
Miscellaneous
Lipedematous alopecia

Table 2. Etiology of secondary cicatricial alopecia.

Another form of alopecia that is characterized by "biphasic pattern" also involves the scarring processes pathologically. Clinical observations suggest that this form of alopecia may be irreversible. Examples of the clinical diseases that can be categorized in this form are known as "Late-stage nonscarring alopecias" including alopecia areata, patterned hair loss, and traction alopecia, etc. Recent report indicated that the occurrence of biphasic alopecia can also be iatrogenic [13].

3. Clinical features of cicatricial alopecia

According to the clinical course, physicians tend to classify all forms of cicatricial alopecias into unstable group, meaning there is an increased recurrence even with the treatment, and stable group, referring to the forms of cicatricial alopecia that have a low recurrent rate after treatment. The formal form usually includes lichen planopilaris, pseudopelade of Brocq, and discoid lupus erythematosus, whereas the latter form includes isolated traumas, burns, infection, and prior surgery-induced alopecias.

The clinical treatment options for cicatricial alopecia are summarized in **Figure 1**.

3.1. Characteristics of primary cicatricial alopecia

Several factors may have associated with the distribution of primary cicatricial alopecia throughout the world. For example, lymphocytic form dominants among North and South American and Iranian patient groups, whereas neutrophilic form is the dominant one among Chinese patient group [14, 15]. The occurrences of dissecting cellulitis and acne keloidalis nuchae may have close association with genetic background and are seen more frequently in patients of African descent. Sex is another factor believed to be related with the prevalence of primary cicatricial alopecia. Folliculitis decalvans, dissecting cellulitis, and acne keloidalis nuchae are more common in males, while central centrifugal cicatricial alopecia, lichen planopilaris, discoid lupus erythematosus, and pseudopelade of Brocq have a female predominance. In addition, discoid lupus erythematosus, dissecting cellulitis, and acne keloidalis nuchae are frequently seen in younger patients, whereas central centrifugal cicatricial alopecia, lichen

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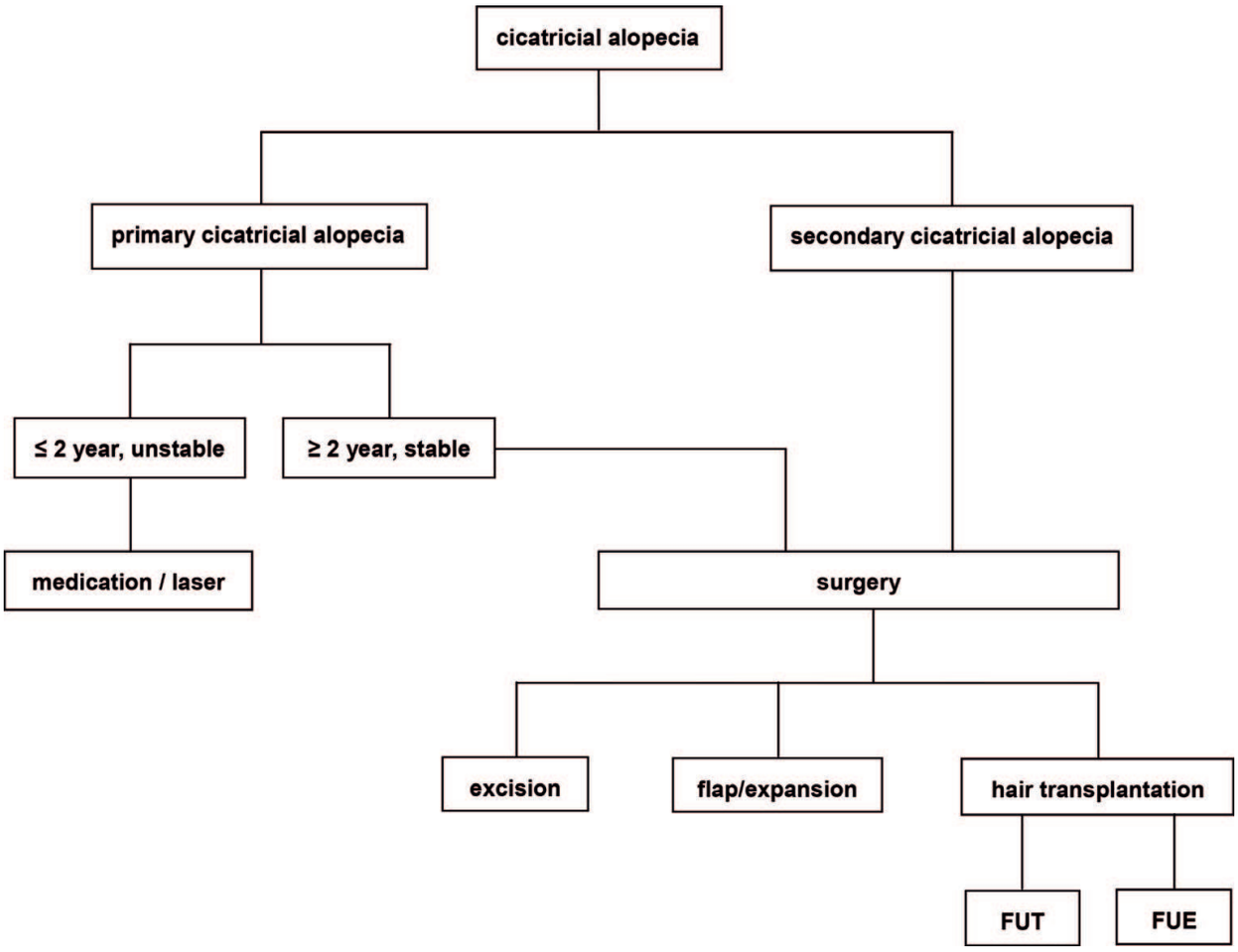

Figure 1. Schematic diagram of treatment options.

planopilaris, and folliculitis decalvans tend to be distributed among older patients. Lastly, there are correlations between certain forms of cicatricial alopecia and the patterns of the baldness. For example, unifocal-ragged border of bald area may associate with central centrifugal cicatricial alopecia and discoid lupus erythematosus, multifocal-interconnected pattern may often be seen in lichen planopilaris and folliculitis decalvans, and multifocal-separated pattern may be one of the characteristics of clinical feature of dissecting cellulitis.

3.2. Lymphocytic cicatricial alopecia

3.2.1. Chronic cutaneous lupus erythematosus (classic discoid lupus erythematosus)

3.2.1.1. Clinical features

This is one of the major forms of cicatricial alopecia among European patients and typically affects women with age between 20 and 60 years old [9, 16]. It presents with erythematous scaly papules with characteristic follicular plugging (**Figure 2**). The lesions evolve into hypo- or depigmented atrophic plaques with peripheral hyperpigmentation, overlying telangiectasias, and loss of follicles. Systemic lupus erythematosus (SLE) associates with 20% of cases [17], and the detections of antinuclear antibodies are positive in approximately 20% of cases [16].

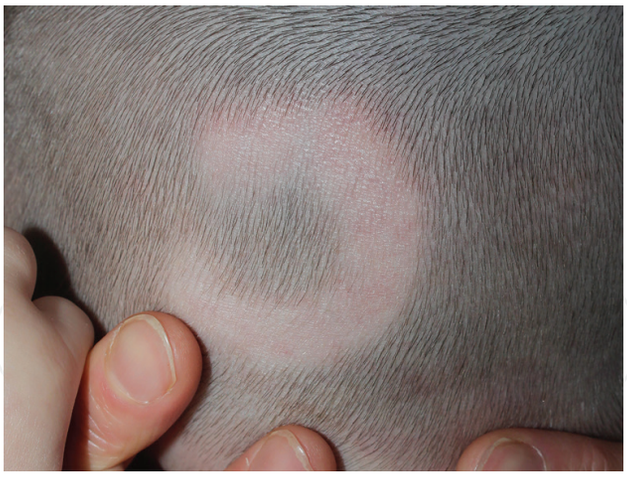

Figure 2. Alopecia at occiput region in a patient with cutaneous lupus erythematosus.

3.2.1.2. Pathological features

Interface dermatitis with epidermal atrophy or hyperplasia in the hypertrophic variant of chronic cutaneous lupus erythematosus; ortho-hyperkeratosis with areas of parakeratosis and follicular plugging; an inflammatory lymphocytes infiltrate with admixed plasma cells distributed around the superficial and deeper dermal vasculature as well as adnexal structures and scattered within the interstitium; early destruction of sebaceous glands; replacement of the follicle with fibrous tissue in late stages; hair fiber granulomas on occasion; occasional inflammatory infiltrate into the subcutis with lymphoid follicle formation [18].

3.2.1.3. Featured stainings

Periodic acid-Schiff (PAS) stains showing thickened PAS-positive basement membrane zone; mucin deposition in reticular dermis or perifollicular scarring tissues; immunofluorescence staining positive signals of IgG, IgM, and complement C3 along the dermal-epidermal or follicular epithelial-dermal junction [19, 20].

3.2.1.4. Treatment

First-line systemic therapy: hydroxychloroquine (HCQ).

3.2.2. Lichen planopilaris (LPP)

3.2.2.1. Clinical features

The lesion appears at the scalp in about half of the cases. Some of the lesions may develop to mucous membranes [2]. Clinically, hair loss can be patchy or diffuse and presents with perifollicular erythematous papules and acuminate hyperkeratotic follicular spines (**Figure 3**). The disease is most active at the hairbearing periphery of the alopecic patch [21].

Lichen planopilaris and frontal fibrosing alopecia are slowly progressive with episodes of worsening. Systemic therapy is strongly recommended if symptoms or hair loss is persistent or progressive.

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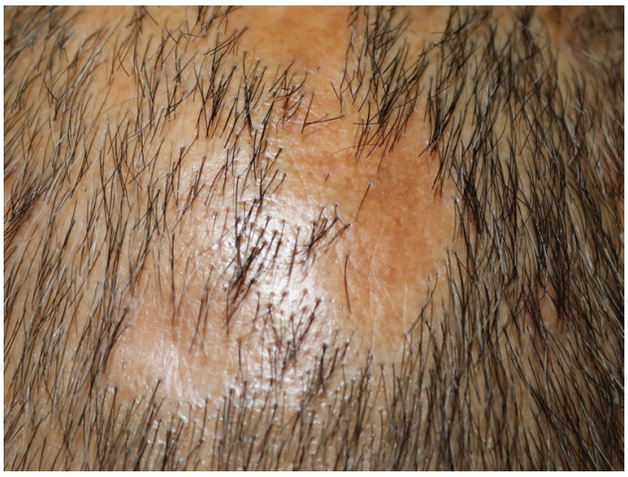

Figure 3. Scalp lesion of lichen planopilaris leads to alopecic patches.

3.2.2.2. Pathological features

Lichenoid band-like infiltrate in the infundibulum, isthmus, and variably the interfollicular epidermis regions; cytoid bodies, basal vacuolization, pigment incontinence, and Max Joseph spaces along the follicular epithelium; follicular plugging; concentric lamellar fibroplasia, loss of sebaceous glands and follicles [22, 23].

Vague mucin deposition in dermis; loss of elastic tissue staining of the upper third of the fibrous tract, and associated destruction of the elastic sheath in late-stage lesions.

Nonspecific IgM within cytoid bodies along the upper hair follicle on direct immunofluorescence observation [24].

3.2.2.3. Treatment

First-line therapy: systemic medications, tetracycline antibiotics, or HCQ. Tetracycline 500 mg twice daily and doxycycline hyclate 100 mg twice daily. The mechanism of action is thought to be due to the anti-inflammatory benefits of the tetracycline antibiotics. The medications are recommended to be limited to 6 months. The efficacy of HCQ in LPP is identical to that of tetracyclines [25].

3.2.3. Frontal fibrosing alopecia (FFA)

3.2.3.1. Clinical features

Frontal fibrosing alopecia, as described by Kossard, is a scarring alopecia that occurs most often in postmenopausal women [26]. It is clinically characterized by a progressive recession of the frontal and temporal hair lines with follicular hyperkeratosis, perifollicular erythema, and loss of follicular ostia [2]. More than half of the FFA patients also have eyebrow hair loss.

3.2.3.2. Pathological features

Histopathology shows a lichenoid reaction against miniaturized hair follicles.

3.2.4. Graham-Little syndrome

Patchy, progressive scarring alopecia of the scalp, nonscarring alopecia of axillary and pubic hair, and the presence of widespread horny follicular papules on the trunk and limbs are clinical traits of Graham-Little syndrome [2].

3.2.5. Classic pseudopelade (Brocq)

3.2.5.1. Clinical features

Classic pseudopelade is a rare, slowly progressive hair disorder of typically the most common form observed in middle-aged Caucasian women. It is presented footprints in the snow to round hypopigmented atrophic alopecic plaques resembling "footprints in the snow" [27].

3.2.5.2. Pathological features

Perifollicular lymphocytic infiltrate, with eccentric atrophy of the outer root sheath epithelium, prominent concentric lamellar fibroplasia, loss of sebaceous glands and follicles, and hair-shaft granulomas [15].

Elastic fibers are markedly thickened in pseudopelade of Brocq. Direct immunofluorescence usually negative but may reveal scant finely granular IgM along the basement membrane zone of the follicular infundibulum [28].

3.2.6. Central centrifugal cicatricial alopecia

3.2.6.1. Clinical features

It is commonly seen in young to middle-aged women of African-American descent with a prevalence of 3–6% [29–31]. It presents progressive alopecia over the crown and vertex that expands centrifugally without overt inflammation and with tufting and perifollicular hyperpigmentation.

3.2.6.2. Pathological features

Premature desquamation of the inner root sheath; perifollicular lymphocytic inflammation of the infundibulum and isthmus; eccentric atrophy of the outer root sheath epithelium, concentric lamellar fibroplasia, and hair fiber granulomas within fibrous tract remnants [32].

Preserved elastic sheath and thickened dermal elastic fibers. Direct immunofluorescence usually negative [33].

3.2.7. Alopecia mucinosa

3.2.7.1. Clinical features

Papules and plaques of hair loss with variable dysesthesia and anhidrosis on the eyebrows, scalp, trunk, and limbs. Presents in all age groups. May be benign or associated with lymphoma (especially mycosis fungoides).

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3.2.7.2. Pathological features

Lymphocytic inflammation around perifollicle; variably atypical lymphocytes; restricted T-cell lineages seen in benign and malignant forms.

Direct immunofluorescence negative.

3.2.7.3. Treatment

Tetracycline antibiotics typically are helpful although not recommended for systemic therapy. Improvement may be seen within 2–6 months followed by dose reduction [34].

3.2.8. Keratosis follicularis spinulosa decalvans

3.2.8.1. Clinical features

An X-linked disorder of cornification with the onset of the alopecia in the teenage years. Acuminate keratotic follicular papules and pustules on the scalp, eyebrows, and eyelashes, keratosis pilaris on the trunk and extremities, photophobia, and corneal dystrophy as the clinical characteristics.

3.2.8.2. Pathological features

Follicular plug with compact hyperkeratosis and hypergranulosis; upper follicle lymphocytic infiltrate; concentric lamellar fibrosis, hair shaft granulomas, and fibrous follicular tract remnants.

3.2.8.3. Treatment

Etretinate, isotretinoin, oral antibiotics, and dapsone are reported medications [35].

In summary, lymphocytic primary scarring alopecias generally can be treated with tetracycline antibiotics, HCQ (hydroxychloroquine), or immunosuppressant medications such as corticosteroids, cyclosporine, and mycophenolate mofetil. Auxiliary drugs are also used specifically for some types of diseases. For example, pioglitazone or 5-alpha reductase inhibitors are used for LPP or FFA, respectively. Treatment response can be seen typically between 6 and 12 months, and gradual taper may result in sustained remission after discontinuation of oral therapy [7, 10].

3.3. Neutrophilic cicatricial alopecia

3.3.1. Folliculitis decalvans

3.3.1.1. Clinical features

Occurs primarily in young and middle-aged adults with a slight predominance in men. Multiple hairs emerge from a single follicular orifice in a pattern known as "tufted hair folliculitis." Erythematous follicular papules or pustules on the crown progress to pseudopelade-like round alopecic patches with pustules at the advancing margins and with

polytrichia. *Staphylococcus aureus* is commonly isolated from primary lesions. Dermoscope examination reveals low hair density and loss of follicular ostia, thinned shafts of the remaining hairs [24].

3.3.1.2. Pathological features

Follicular plugging and intra/perifollicular neutrophilic infiltrate of the upper and middle portions of the hair follicle; follicular rupture with infiltrates of lymphocytes, histiocytes, and plasma cells; neutrophilic abscess is common; hair shaft granulomas prominent; late-stage replacement of hair follicles with scarred fibrous tracts. Existence of plasma cells has diagnostic significance in advanced cases.

3.3.1.3. Treatment

First-line treatment: oral administration of tetracycline, doxycycline, minocycline, erythromycin, and clindamycin alone or in combination with rifampin. However, relapse is common after discontinuation of these antibiotics [36].

3.3.2. Dissecting cellulitis/folliculitis (perifolliculitis abscedens et suffodiens)

3.3.2.1. Clinical features

Commonly seen in younger men of African Americans with inflammatory plaques and nodules, often associated with formation of sinus tracts that exude a purulent discharge. The process commonly begins on the occiput or vertex and often progress to involve the entire scalp (**Figure 4**). Recurrent bacterial infections and disordered keratinization are important causes [19].

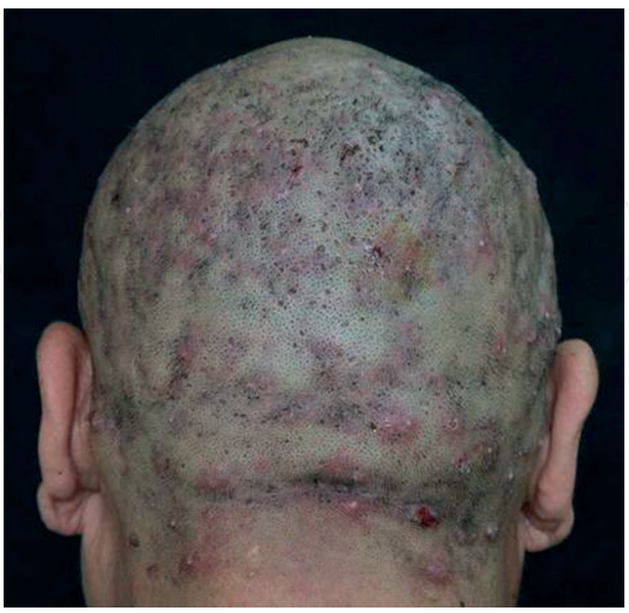

Figure 4. A patient with dissecting cellulitis/folliculitis presents with inflammatory plaques, nodules, and purulent discharges over the entire scalp.

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3.3.2.2. Pathological features

Follicular plugging and collections of neutrophils at the follicular ostia; extensive abscess formation and extensive dermal fibrosis.

3.4. Mixed cicatricial alopecia

3.4.1. Folliculitis (acne) keloidalis

3.4.1.1. Clinical features

Most frequently in African postpubertal males with follicular erythematous papules and pustules that progress to hairless keloid-like nodules.

3.4.1.2. Pathological features

Neutrophilic or lymphoplasmacytic perifollicular infiltrate; thinned outer root sheath with reparative concentric lamellar fibroplasia; follicles are destroyed, hair-shaft fragments are extruded; hair-shaft granulomas or microabscess formation are prominent [2].

3.4.2. Folliculitis (acne) necrotica

3.4.2.1. Clinical features

Lesions present as crops of red-brown papules and papulopustules that undergo necrosis and become punched out, depressed scars after eventual healing.

3.4.2.2. Pathological features

Fragments of hair shaft; scattered neutrophils are present in the superficial dermis where follicular epithelium undergoes necrosis [7].

3.4.3. Erosive pustular dermatosis

3.4.3.1. Clinical features

Primarily affects elderly women and presents with extensive, boggy, crusted, erosive plaques on the scalp. It is thought to be triggered by local trauma sometimes months to years prior to the appearance of lesions or occur as a result of autoimmune disease [37].

3.4.3.2. Pathological features

Nonspecific findings in biopsy samples indicate the epidermis may be ulcerated or appear atrophic or hyperplastic. A mixed patchy dermal inflammatory infiltrate is seen. Suppurative folliculitis, intraepidermal, and subepidermal neutrophil infiltrates are common. Dermal fibrosis may focally replace the follicles or may diffusely involve the dermis, depending on the extent of inflammation. Scattered naked hairshaft granulomas are also seen in later stages.

3.5. Characteristics of secondary cicatricial alopecia

The causes of secondary cicatricial alopecia include even more diverse forms of trauma and inflammatory injuries. Of note, iatrogenic cause of hair loss such as with esthetic surgery is a concern among both patients and physicians. Currently, there is no effective treatment protocol for any subtypes of secondary cicatricial alopecia except to attenuate the development of inflammation processes initiated by topical tissue damages or infection. Medications used for these purposes include high-potency topical corticosteroids, immunosuppressants, and antibiotics. Nevertheless, permanent hair loss may eventually be the outcome, and the baldness

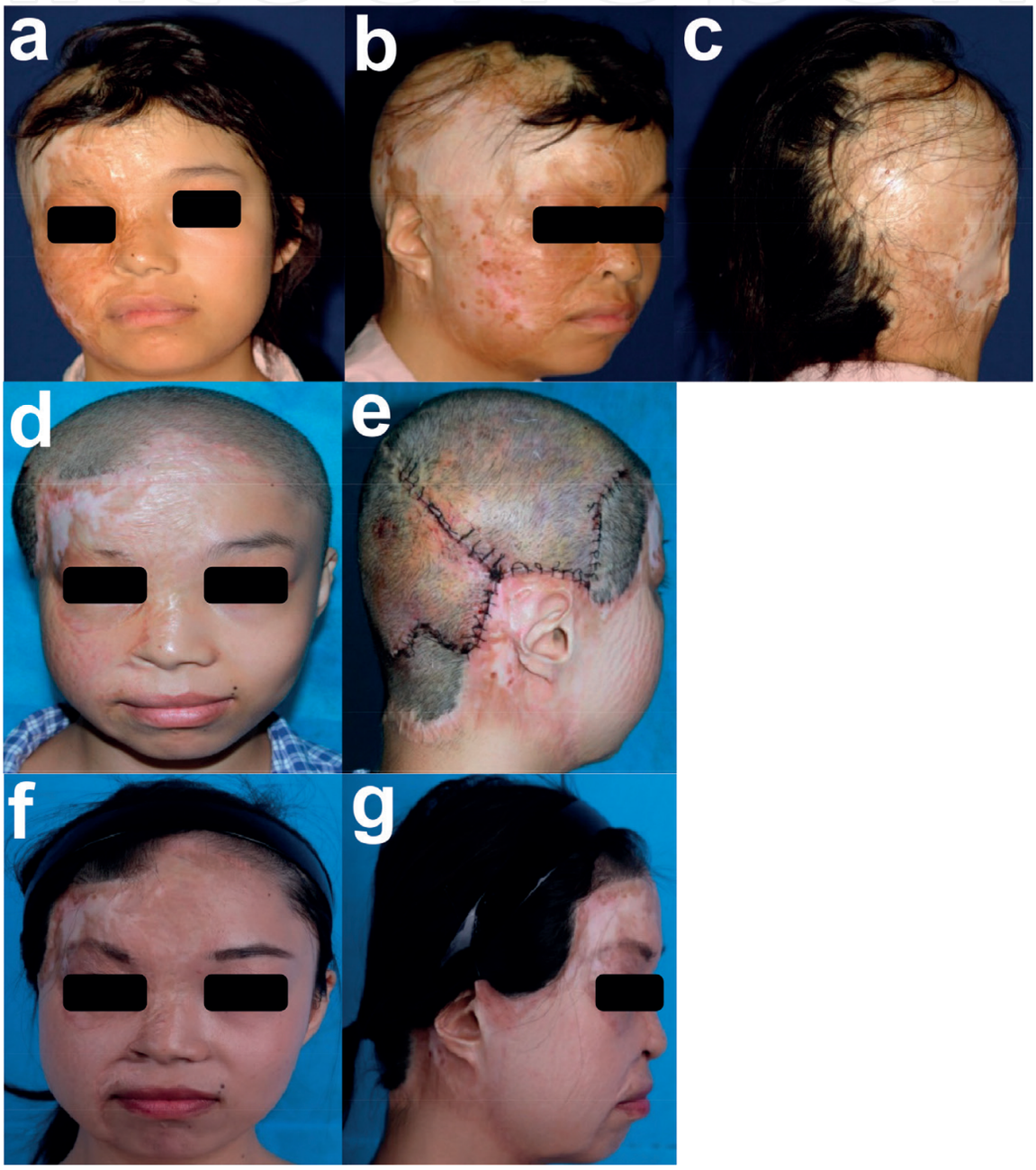

Figure 5. Reconstruction of secondary cicatricial alopecic region with expanded scalp flaps. (a–c) Photographs of a patient with thermal injury induced alopecia; (d, e) Photographs taken at post-operative day 7 after reconstruction of bald areas with expanded skin flaps; and (f, g) Follow-up photographs taken at month 29 post-operatively.

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would become evident if the area of the secondary cicatricial alopecia is extensive (**Figure 5**). Therefore, autologous hair transplantation and replacement of the bald skin with skin flaps that have hairs with satisfactory density are acceptable procedures for this form of alopecia [2].

3.6. Biphasic alopecias

The term "biphasic alopecia" includes some conditions where cicatricial alopecia becomes apparent in the late stages of an otherwise nonscarring form of alopecia. Alopecia areata, androgenetic alopecia, and traction alopecia may belong to this category. Alopecia areata can result in fibrosis in 10% of cases, while in advanced stages of androgenetic alopecia, vellus hairs also disappear and the alopecia becomes permanent [2]. We have noticed that esthetic filling with hyaluronic acid (HA) can induce biphasic alopecia that may leave permanent hair loss in the severely necrotic lesion region, whereas hair regrowth was found in possible less ischemic area (**Figure 6**).

3.7. The application of minoxidil

Minoxidil has demonstrated an antifibrotic action and believed to be efficient in the early course of some dermatoses leading to scarring alopecia, such as scalp burning disease. Mechanistically,

Figure 6. Hyaluronic acid filling in the left temple region results in the skin necrotic and ischemic lesion leading to an area of a permanent hair loss surrounded by regions with slow-restoration of hair regrowth [13]. (a) Complete hair loss was seen in the patient's left temple area after HA injection. A HA injection induced necrotic skin crust surrounded by bald skin area at day 22 is shown; (b) near healed prior necrotic skin and surrounding skin still showed no sign of hair regrowth at post-HA injection day 42 post-HA injection; (c) partial hair regrowth was seen in the bald area except the prior necrotic crust covered region at post-HA injection day 74; and (d) a view of long-term recover of hair regrowth surrounding a permanent bald area at post-HA injection day 209.

scalp sulfotransferase changes minoxidil into minoxidil sulfate, which is thought to be the active form of the molecule. The variations of sulfotransferase activity between individuals may explain the interindividual variations in minoxidil efficiency. Minoxidil acts by shortening telogen phase and thus causing the quiescent hair follicles to enter prematurely into anagen phase, resulting in telogen effluvium after the initiation of minoxidil therapy, although such effect of minoxidil may increase hair length and diameter. Some basic research results suggest that minoxidil can intervene on the potassium channels of the vascular smooth muscles and hair follicles, which may induce the following effects: (1) stimulation of the microcirculation near the hair follicles by inducing arteriolar vasodilation, which may cause hair growth. Minoxidil induces the expression of vascular endothelial growth factor (VEGF) which increases vascularization around the hair follicles, thus contributing to hair growth; (2) activation of the prostaglandin-endoperoxide synthase one which stimulates hair growth; (3) inhibition of the effects of androgens on the androgen-sensitive hair follicles; and (4) direct stimulating action on the hair follicles: Minoxidil may act as an 'epidermal growth factor' on matrix cells delaying their aging, thus prolonging the duration of anagen phase, probably via the activation of the beta-catenin pathway [38–40].The effect of minoxidil becomes evident after approximately 8 weeks post-treatment, and the maximal effect may be seen after 4 months. Most of the clinical responders to minoxidil have alopecia with the onset of less than 5 years, particularly among young adults, with their follicles not deeply miniaturized [41].

Minoxidil is well tolerated. However, propylene glycol contained in the liquid form (solution) of minoxidil may be the cause of some adverse effects reported by patients that include: (1) minoxidil-induced telogen effluvium: the shortening of telogen phase by minoxidil causes marked shedding; (2) skin irritation: with erythema, discomfort, and burn sensation; (3) scaly changes of the scalp: due to irritation or exacerbation of seborrheic dermatitis; (4) isolated itching; (5) allergic contact dermatitis: with erythema, eczematous skin reaction, and itching. Minoxidil and propylene glycol are the major allergens in allergic contact dermatitis. Patch testing may be helpful to reveal the causative agent. In case of allergic contact dermatitis to propylene glycol, minoxidil foam (i.e., not containing propylene glycol) may be used; (6) localized or generalized hypertrichosis: this effect seen during oral minoxidil treatment may also be observed with topical form. It is probably related to the prolongation of anagen phase. This effect seems to be more commonly encountered with 5% minoxidil than 2% minoxidil.

Percutaneous toxicity is exceptional after a conventional use of minoxidil which has no known antidote for minoxidil massive oral ingestion. Accidental oral ingestion of minoxidil results in mild vomiting and rarely requires hospitalization. However, cases of hypotension, tachycardia, and/or electrocardiographic changes after accidental ingestion have been reported. Refractory hypotension may be managed by intravenous fluids and vasopressor agents. Gastric wash and activated charcoal may be indicated to prevent systemic toxicity in massive accidental ingestion of minoxidil.

3.8. Hair transplantation

The hair transplantation replaces the lost hairs with autologous hairs harvested from donor sites. Based on clinical experience, another 2 years may be required before the recipient site fully supports the survival and growth of hair grafts after the disease is stabilised. For limited area of hair loss, select local skin flap. For large bald area, expanded scalp skin flap can be selected or select hair transplantation technique [42, 43] (**Figure 5**).

For transplantation procedure, here we briefly introduce follicular unit extraction (FUE) technique. It is the treatment of choice in instances where there is good availability of donor hair and vascular circulation [44]. Briefly, in FUE surgery, there is no linear scar but instead each extraction site leaves a small round dot scar that can be hidden even with shorter hairstyles compared to a strip scar (**Figure 8**). The punches vary in size but generally are in the range of 0.75–1.2 mm in diameter attached to either a hand-held manual device, a hand-held mechanized drill device or an automated robotic device. The recommended density of the site in the recipient area is 15–20 FU/cm^2 in areas with low perfusion and 20–30 FU/cm^2 in areas with sufficient blood perfusion. The integrated grafts started to grow 4–5 months after the surgery and most entered the anagen phase approximately 1 year postoperatively (**Figure 7**). For hair loss from burn injury, successful treatment with hair transplantation was reported although the hair follicle graft survival rate in scar tissue can be varied significantly [43–45].

Advantages of FUE include the absence of suture wounds and linear scars, less bleeding, and less postoperative discomfort than follicular unit transplantation. In addition, it is suitable for patients with less scalp laxity and poor wound healing. Furthermore, scarring at each individual site may limit the possibility of harvesting hair in the same area in the future. Moreover, the hair transection rate is higher than in follicular unit transplantation and buried tissue can cause inflammation and cyst formation [44].

Figure 7. Autologous hair transplantation. (a) Burns induced hair loss in the temple region; (b) seven days after hair transplantation by FUE technique; and (c, d) photographs of hair regrowth at month 11 after hair transplantation.

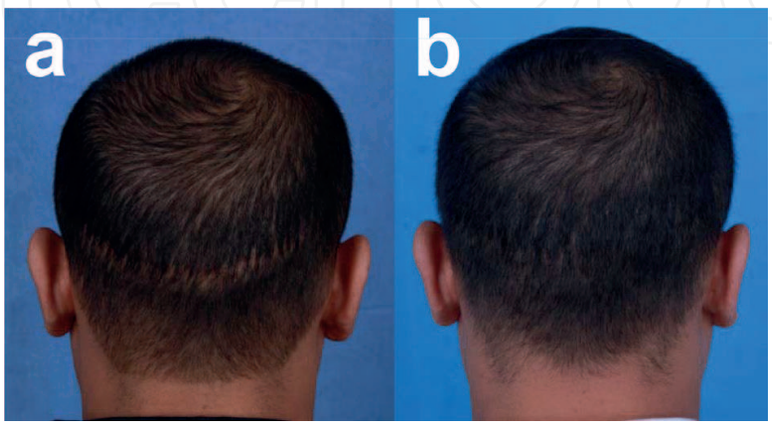

Figure 8. Linear scar at the donor site resulted from FUT procedure. (a) A linear scar with loss of hair is visible at the occiput donor region after FUT procedure and (b) the scar is invisible after hair implantation by a FUE procedure.

Disadvantages of this technique are that large harvesting sessions require the entire donor area to be shaved and the grafts tend to have less tissue around them and therefore more care is needed in handling them. Only with multiple or ill-planned procedures, there will be thinning out of the donor area.

Currently, the recipient holes or slits are made using either a punch, scalpel, different types of needles, or automated devices. A novel technique based on CO_2 laser tissue ablation was introduced in 1994 by Unger and David. However, one major possible disadvantage is the known thermal coagulation zone more or less present in all CO_2-based laser systems. Such thermal damage may raise concerns of reduced blood perfusion present in treated scar tissue [46].

The Er:YAG laser produces energy in the mid-infrared light spectrum at 2940 nm. This wavelength has 10–15 times greater water absorption than a CO_2 laser with an emission at 10,600 nm. Together with a pulse below the thermal relaxation time of skin, the Er:YAG laser allows "cold"-ablation with very little vaporization and desiccation. Minimal damage of the surrounding tissue combined with the precision of a laser should make this a valuable instrument for creating holes or slits for hair transplantation in cicatricial alopecia [46].

4. Conclusions

Cicatricial alopecia refers to a diverse group of local and systemic diseases in which hair loss is one of the outcomes. Although efforts have been made through medication treatments to counter the pathologic progression that would damage and replace the follicular unit with fibrous scarring, the efficacy of each treatment protocol may still lack of the supports through evidence-based studies, therefore, warranting further basic and clinical investigation. In contrast, hair transplantation has demonstrated more predictable and satisfactory outcome. Nevertheless, preparation of scalp recipient tissue with medication prior the surgery and post-surgery care with professional assistance are imperative for the survival and long-term maintenance of hair grafts.

Conflict of interest

The authors declare no conflict of interests.

Acronyms and abbreviations

Brocq	classic pseudopelade
CCCA	central centrifugal cicatricial alopecia
CK	cytokeratin
CO_2	carbon dioxide
FD	folliculitis decalvans

FFA	frontal fibrosing alopecia
FUE	follicular unit extraction
HA	hyaluronic acid
HCQ	hydroxychloroquine
KFSD	keratosis follicularis spinulosa decalvans
LPP	lichen planopilaris
MHC	major histocompatibility complex
PCAs	primary cicatricial alopecias
PPAR-γ	peroxisome proliferator-activated receptor-γ
PPB	pseudopelade of Brocq
PAS	periodic acid-Schiff
SLE	systemic lupus erythematosus
VEGF	vascular endothelial growth factor

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