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Alopecia as a systemic disease

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Abstract Alopecia is a skin condition of great social and psychologic impact. Primary alopecia originates from the hair follicles and usually does not have systemic manifestations; however, secondary alopecia can affect the hair follicles in the setting of systemic diseases, medications, and external trauma. Connective tissue diseases, granulomatous diseases, bullous diseases, infections, and tumors are some of the systemic diseases that will be covered in this review. Trichoscopy is a useful noninvasive tool that can help with the diagnosis in the office and can guide the selection of the optimal site for the scalp biopsy. Histopathology is the ultimate tool for the diagnosis in most cases of secondary alopecia and can be performed on vertical and horizontal sections. In most cases, treating the underlying condition is the single most important strategy, but topical treatments for the alopecia are also applied.

A brief historical perspective/background

Alopecia has a captivating nomenclature, first derived from the ancient Greek word "alopex," which referred to fox-mange. Fox-mange, or sarcoptic mange, is caused by the *Sarcoptes scabiei* mite infection[1,2] and results in loss of fur of the fox, intense pruritis and dermatitis, secondary bacterial infections, and eventually death.[2]

In humans, alopecia, or hair loss, has dated back to biblical times. In the Old Testament, the prophet Elisha was teased by children for having a "bald head."[3] Although the pattern of his hair loss was unknown, this documentation provides evidence that this difficult-to-treat condition has been affecting humans for thousands of years.

Hippocrates, Julius Caesar, and King Louis XIII are more historical figures who were not immune to alopecia.[4] Many natural remedies, from minced mice, horse teeth, and bear grease used by Julius Caesar, to nettle, dandelions, and roots in 20th-century England, have been applied in the hopes of promoting hair growth and without much benefit.[4,5] Eventually, Caesar donned a laurel wreath and the French king a toupee, to camouflage their balding heads.

Classification

The answer to the question of whether alopecia may be considered a systemic disease is that although alopecia itself does not cause systemic disease, it can be a presentation of systemic disease. Alopecia can be divided into primary alopecia, or disease that originates from the hair follicle, and secondary alopecia, which is the result of systemic diseases, medications, or trauma affecting the hair follicles. Primary alopecia is out of the scope of this presentation. The most common causes of secondary alopecia are summarized in Table 1.

Connective tissue disease

The most common pattern of hair loss in connective tissue disease is telogen effluvium. Connective tissue diseases are

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Table 1 Most common causes of secondary alopecia

Connective tissue disease	Lupus erythematosus
	Dermatomyositis
	Systemic sclerosis
Bullous disease	Bullous pemphigoid
	Pemphigus
	Epidermolysis bullosa
Granulomatous disease	Sarcoidosis
Infection	Leprosy
	Syphilis
	Herpes simplex infection and herpes zoster
	Tinea capitis
Malignancy related	Lymphoproliferative disorders
	Alopecia neoplastica
Postoperative	Postoperative alopecia
Miscellaneous	Amyloidosis

associated with high levels of proinflammatory cytokines during flares, which negatively affects the hair growth cycle, causing diffuse "inflammatory shedding."[6] Other manifestations include diffuse thinning and scarring alopecia. The most common causes of hair loss in autoimmune connective tissue diseases are lupus erythematosus, dermatomyositis, and morphea.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a disease well known for its ability to affect virtually every organ. Nonscarring alopecia is now part of the newly proposed criteria in the American College of Rheumatology classification criteria for SLE.[7]

The disease's cutaneous manifestations include the classic malar dermatitis and photosensitivity, discoid lesions, nasal and oral ulcers, and alopecia. The mechanism behind alopecia in SLE has not been fully elucidated. In previous studies, although no correlation between SLE disease activity index (SLEDAI) and alopecia was found, there was a statistically significant association between alopecia and the cutaneous manifestations of SLE.[8,9]

The most common presentations include diffuse telogen effluvium (65%), patchy nonscarring alopecia (15%), and hair line recession due to lupus hairs.[10] Diffuse telogen effluvium usually correlates with disease activity and can be associated with burning and itching. Lupus hair presents as short, coarse, dry hair on the frontal hairline on physical examination and as hair shaft thinning, hypopigmentation, and interfollicular telangiectasias on trichoscopy.[11]

Patchy nonscarring alopecia in SLE (clinically noninflammatory alopecic patches of LE) occurs in about 15% of the patients and presents as hairless patches usually without visible erythema, thus mimicking alopecia areata (AA) (Figure 1a).[10] This type of hair loss is possibly related to local vasculitis and has the potential for complete regrowth. Trichoscopy is very helpful for distinguishing it from AA, as there is absence of exclamation hairs and other dystrophic hairs.[12] Histopathology shows deep periadnexal inflammatory infiltrate with formation of germinal-center–like lymphoid follicles and a lack of superficial inflammation (Figure 1b). Control of the systemic disease is the single most important treatment; however, topical steroids and minoxidil can contribute to controlling the hair loss and achieving complete regrowth.

Discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is the most common form of cutaneous lupus and can present with a scarring alopecia with LE-specific changes on histopathology.

Up to 60% of patients with DLE have scalp involvement.[11] Clinical examination shows well-demarcated, erythematous, scaly plaques with induration, atrophy, and follicular plugging (Figure 2a). The lesions may be pruritic or tender. The most common trichoscopic findings are follicular red dots, large yellow dots with interfollicular arborizing vessels, monstrous vessels, blue-gray dots, and follicular keratotic plugs[13] (Figure 2b). Biopsies demonstrate interface dermatitis

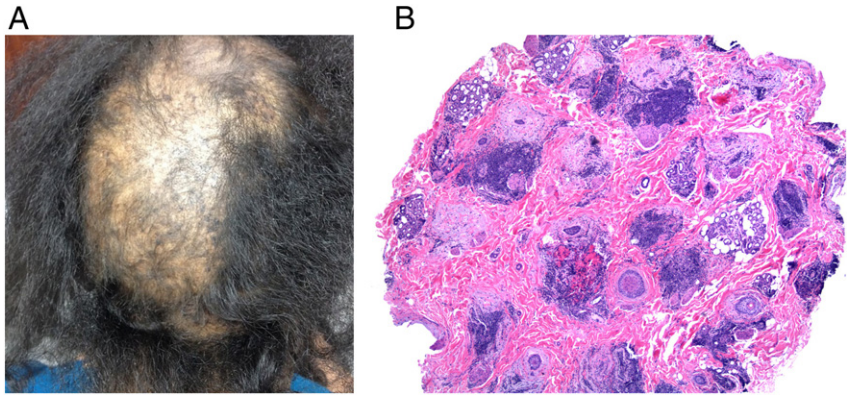

Fig. 1 **(a)** Patchy nonscarring alopecia in a patient with systemic lupus erythematosus. Focal areas of regrowth can be noticed. The patient had complete regrowth after treatment with clobetasol and minoxidil. **(b)** Pathology of nonscarring alopecia in lupus erythematosus reveals deep lymphoid cell infiltrate in germinal-center-like collections in a periadnexal pattern (hematoxylin and eosin, ×4).

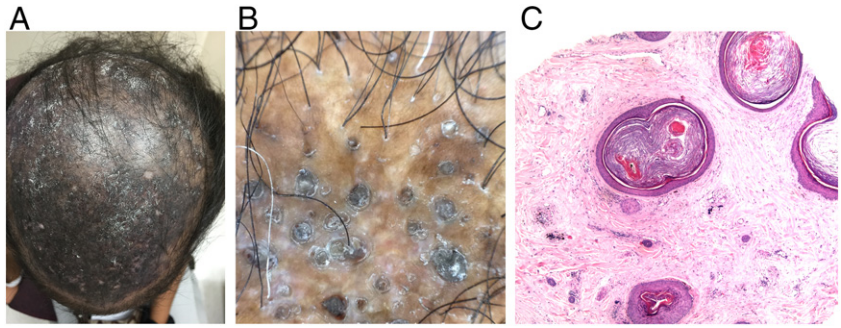

Fig. 2 **(a)** Discoid lupus erythematosus on central scalp presenting as plaques with hyperpigmentation alternating with hypopigmentation and diffuse scaling. **(b)** Discoid lupus erythematosus demonstrates keratotic plugs on trichoscopy (Handyscope, FotoFinder Systems, ×20). **(c)** Discoid lupus erythematosus, lichen planopilaris subtype. Pathology shows interface dermatitis and keratotic plugs in the follicular ostia (hematoxylin and eosin, ×10).

involving the dermo-epidermal junction, thickened basement membrane, periadnexal lymphoid cell infiltrate, and mucin in the dermis and subdermis. A recent study identified two patterns on horizontal sections (AA-like pattern in 52% of the biopsies and lichen-planopilaris–like pattern in 18%) (Figure 2c).[14]

Other scalp presentations of lupus erythematosus

Classic lupus panniculitis or lupus profundus is another presentation of a scarring alopecia in lupus with LE-specific changes on histopathology. It presents usually as erythematous, indurated plaques of linear alopecia with trichoscopic findings significant for large yellow dots, vellus hairs, thick arborizing vessels, and diffuse erythema.[11]

Linear and annular lupus panniculitis of the scalp is very rare and presents as alopecic patches along Blaschko's lines most commonly in the parietal (70%) and frontal regions (45%).[15] Direct immunofluorescence is positive in 70% of the cases for granular deposition of immunoglobulin G (IgG) along the follicular epithelium or basement membrane and can contribute to the diagnosis.[11] Trichoscopy shows many thick arborizing vessels, erythema, large yellow dots, black dots, and perifollicular scales.[11]

First-line therapy for DLE is sun protection, topical and intralesional steroids, topical calcineurin inhibitors, and minoxidil; however, treating underlying disease activity (in cases of associated SLE) is the key to improvement of hair disease. Systemic treatments include oral corticosteroids and hydroxychloroquine. Other systemic medications, such as methotrexate, dapsone, biologics, and intravenous immunoglobulin can also be used as second- and third-line treatments.[16]

Dermatomyositis

Dermatomyositis is an idiopathic inflammatory myopathy that classically causes proximal skeletal muscle weakness along with specific dermatologic findings, including Gottron's papules, heliotrope eruption of the eyelids, facial erythema, poikiloderma in sun-exposed areas, calcinosis cutis, periungual changes including telangiectasias, and scalp involvement that may resemble scalp psoriasis or seborrheic dermatitis.[17] Scalp involvement in dermatomyositis (SDM) usually correlates with a flare of the disease and is typically a nonscarring and diffuse hair loss that may be associated with highly pruritic, scaly, red patches.[18] According to a recent study, about 77% of patients with dermatomyositis suffered from scalp involvement, with erythema being the most common

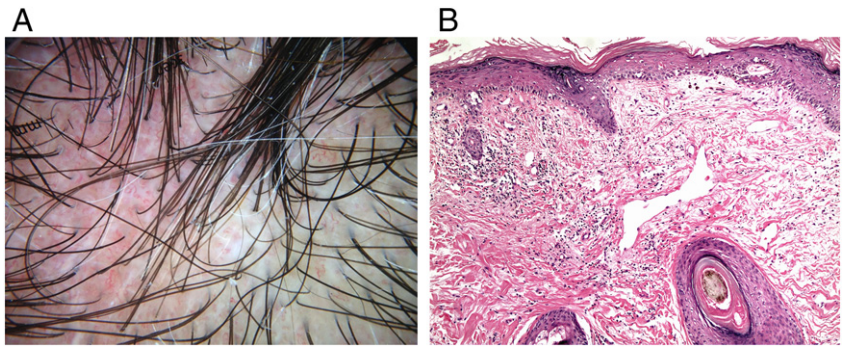

Fig. 3 **(a)** Dermatomyositis of the scalp. Note the arborizing vessels on a background of pale scalp (Handyscope, FotoFinder Systems, ×20; image courtesy Julio Jasso, MD). **(b)** Dermatomyositis of the scalp. On pathology, there is interface dermatitis, mucin in the dermis, and dilated capillaries. Note the hyperkeratosis and the hypergranulosis of the acrosyringium (hematoxylin and eosin, ×10).

physical examination finding, followed by scaling (83%) and pruritis (71%).[19] SDM has previously been described as psoriasiform-like dermatitis due to its flaky, erythematous appearance, which commonly leads to misdiagnoses.[20]

Recent studies have delineated the trichoscopic features and histopathology of SDM. Trichoscopic features reveal enlarged tortuous capillaries, peripilar casts, tufting with three or more hair shafts emerging together, and interfollicular scales (Figure 3a).[19] The most common histopathologic features of SDM in vertical and horizontal sections include diffuse mucin deposition in the papillary dermis, dilated capillaries, thickening of the basement membrane, and interface dermatitis.[21] New findings include acrosyringeal hypergranulosis and hyperkeratosis, which may contribute to pruritis in SDM patients similar to the blocked acrosyringea observed in biopsies from atopic dermatitis (Figure 3b). On horizontal sections, the follicular density is decreased and the terminal-to-vellus ratio is consistent with chronic telogen effluvium.[21] Treatment includes avoiding the sun, topical corticosteroids and calcineurin inhibitors, as well as treating the systemic disease with oral steroids, antimalarials, other systemic immunosuppressive treatments, or intravenous immunoglobulin.

Systemic scleroderma and morphea en coup de sabre

Systemic sclerosis is an autoimmune fibrosing disorder in which fibroblasts increase connective tissue production. Systemic sclerosis has no specific scalp presentation. One study identified polymorphic vessels and avascular areas as the most common trichoscopic findings in the frontal scalp.[22] There are five variants of localized scleroderma (also known as morphea) and include circumscribed (plaque) morphea, generalized morphea, linear morphea, pansclerotic morphea, and mixed morphea.[17] Linear morphea, termed "en coup de sabre" (ECDS), is a cicatricial alopecia that most commonly presents on the scalp in younger patients and can be associated with ocular and/or central nervous system involvement,[23] and 67% of patients are found to have the disease before the age of 18 years.[23] The classic linear scleroderma ECDS demonstrates a well-defined, linear patch of alopecia on the paramedian forehead and frontal scalp along Blaschko's lines.[24]

In addition to this classic presentation, other unusual presentations have been described, such as a linear patch resembling a bruise in a patient with skin of color, two lines on the same side or on either side, three lines on the same side, and annular, patchy involvement of the vertex and occiput.[25–28]

Trichoscopic features are not specific and show loss of follicular openings, pili torti, black dots, and broken hairs. Thick, linear vessels similar to the pattern observed in DLE and dermatomyositis were also observed in two cases.[24] On histopathology, early ECDS presents with perivascular and periappendageal lymphocytic infiltrate.[29] Later, dermal sclerosis is evident along with atrophy of the eccrine glands, collagenous replacement of adipose tissue, and destruction of sebaceous glands[30] (Figure 4). On horizontal sections, there is sclerotic collagen among the follicles that are devoid of sebaceous glands, and there is an increased number of telogen germinal units.

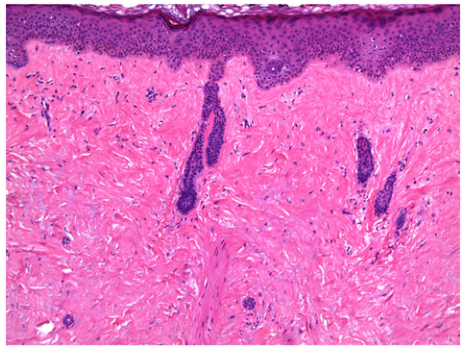

Fig. 4 Linear morphea en coup de sabre shows thick homogenized collagen in the dermis with altered follicular architecture. The only follicular structures present are telogen germinal unit-like structures (hematoxylin and eosin, ×10).

Treatment options include topical therapy, phototherapy, and systemic treatments targeting the increased fibroblasts, collagen production, and inflammation associated with the disease. Topical therapy includes corticosteroids and topical calcipotriene; however, ECDS has deeper sclerotic and inflammatory processes that may not be reached with topical treatment.[31] Systemic therapy with methotrexate with or without prednisone has been reported to have a success rate of about 80%. In a recent review of seven patients with ECDS treated with methotrexate, all patients experienced a halt in disease activity at 2 months of taking the medication.[32] Vitamin D analogs and calcineurin inhibitors can also be used. Lastly, hair transplant, polymethylmethacrylate fillers, or platelet rich plasma may be considered.[33]

Bullous disease

Pemphigus

Up to 60% of patients with pemphigus vulgaris (PV) have scalp involvement; however, the percentage of patients with PV and hair loss is less common, at about 5.4% to 13.8%.[34,35] Anagen effluvium, progressive hair loss with alopecic patches, easily extractable hairs, and tufted folliculitis are the most common hair loss types.[35–40] An increased severity of pemphigus has been described for patients with associated alopecia.[34]

One study described 80 patients with PV and pemphigus foliaceus (PF). Scalp lesions were identified in 65% (52/80), and alopecia was identified in 13.8%. For all patients, the pemphigus disease area index (PDAI) score was measured and was found to be significantly higher in pemphigus associated with alopecia than for patients without pemphigus-associated alopecia. Complete clinical remission was also more common for patients without associated alopecia. Anti-desmoglein 1 (anti-Dsg1) antibodies were higher in patients

presenting with alopecia.[34] In a second study with 52 patients found to have pemphigus, a positive correlation between anti-Dsg1 antibodies and anagen hair loss was found[41]; therefore, pemphigus-associated alopecia could be considered a marker of disease severity of PV,[34,37] and the normal anagen effluvium can be considered a Nikolsky sign of the scalp.[39]

Concomitant bacterial infection has been demonstrated in patients with PV and alopecia.

Easily extractable hairs could be caused by a combined effect of infection and acantholysis mediated by antidesmoglein antibodies as desmoglein 3 is important for the anchoring of the telogen hairs.[35,38,40,42]

On trichoscopy, nonscarring alopecia, developing over severely compromised scalp with erythematous scaling and crusting, has been reported in patients with PF.[43] Extravasation, yellow crusts, dotted vessels surrounded by a white halo and vessels are the most common features.[44] A case of nonscarring alopecia in a patient transitioning from PF to PV has also been reported and resolved after treatment with steroids and concomitant normalization of anti-Dsg3 enzyme-linked immunosorbent assay (ELISA).[45]

Histopathology shows acantholysis extending from the infundibulum to the suprabulbar region in anagen hair follicles and cleft formation in the outer root sheath.[35,37,46] Direct immunofluorescence shows immune deposits of IgG and C3 in the outer root sheath of the hair follicle.[36,37,47] Another common feature of PV and PF in the scalp is miniaturization of sebaceous glands.[44]

Resolution of scalp and hair involvement has been reported with systemic steroids, rituximab, and intralesional steroid injections.[44]

Pemphigoid

Literature regarding the correlation between bullous pemphigoid and alopecia is scarce. In 1973 a previously healthy patient was reported to have suddenly developed alopecia universalis and, 35 years later, was found to have bullous pemphigoid; therefore, bullous pemphigoid and alopecia universalis were thought to be related due to their autoimmune nature.[48] Mucous membrane pemphigoid or cicatricial pemphigoid has been reported to lead to scarring alopecia in some patients.[49,50] In one report, seven patients presented with chronic blistering conditions leading to scarring.[49] It is now called Brunsting-Perry cicatricial pemphigoid and is restricted to the scalp only. Clinically, it is characterized by erythematous crusted lesions that may lead to scarring but no milia (compared with epidermolysis bullosa acquisita) (Figure 5a).

Histopathology shows dermo-epidermal separation at the level of the basal lamina, and fibrosis in the dermis with occasional eosinophils. There is also perifollicular fibrosis at the level of the isthmus (Figure 5b). Positive linear IgG staining on the epidermal side is seen under immunofluorescence.[50]

Treatment includes systemic steroids, and steroid-sparing immunosuppressive treatments, as well as topical steroids and topical calcineurin inhibitors in limited scalp involvement.

Epidermolysis bullosa

Hair changes in epidermolysis bullosa simplex (EBS) are not frequently seen. Few reports of alopecia universalis and congenital alopecia have been described in patients with lethal acantholytic EB and EBS with muscular dystrophy.[51,52] One report described nonscarring alopecia occurring in a 28-year-old woman with EBS.[53] Two cases of diffuse alopecia in patients with EBS with muscular dystrophy secondary to PLEC mutation encoding the cytolinker protein plectin have been described.[52,54]

Patients with EBS secondary to keratin mutations typically do not manifest alopecia. If these patients present with telogen effluvium secondary to anemia due to blistering or sepsis, the hair loss will stop and regrow once the cause is reversed.[55]

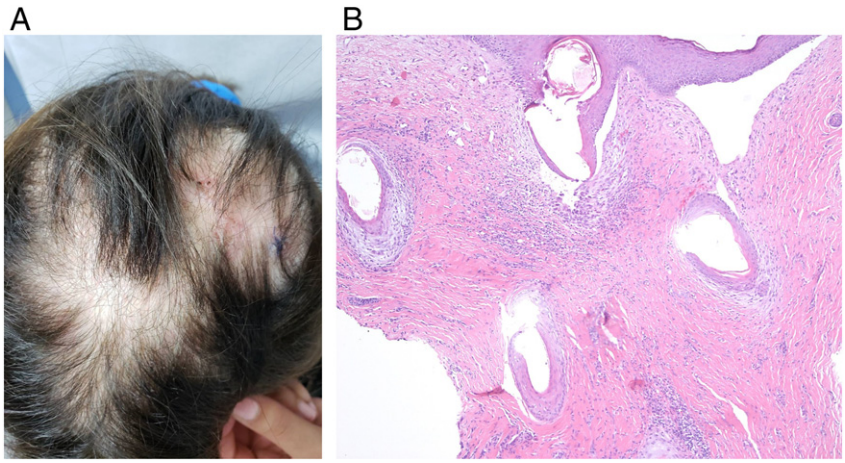

Fig. 5 **(a)** Brunsting-Perry cicatricial pemphigoid of the scalp presents as diffuse areas of scarring alopecia with focal erosions and crusts. **(b)** On pathology, there is altered follicular architecture with presence of perifollicular fibrosis and an absence of sebaceous glands. Note the presence of a subepidermal cleft and underlying diffuse fibrosis in the upper dermis (hematoxylin and eosin, ×10).

Junctional EB is positive for mutations in genes encoding laminin-332 and type XVII collagen, and patchy or diffuse alopecia can be frequently seen.[55–58] In dystrophic EB, scarring alopecia secondary to trauma from rubbing and blistering is common.[55] Sparse hair and delayed puberty have been described in some patients with recessive dystrophic EB.[59] Kindler syndrome has not been associated with alopecia probably due to the lack of kindlin protein in hair follicles.[55]

Histopathology in dystrophic and junctional EB types reveals blistering of the lamina lucida and below, causing inflammation and subsequent cicatricial alopecia. Direct and indirect immunofluorescence, as well as indirect immunofluorescence on salt-split skin, is used to exclude BP.[36]

Granulomatous dermatitis

Sarcoidosis

Sarcoidosis is an idiopathic systemic granulomatosis disease characterized by naked granulomas of epithelioid cells that can occur in any organ. Although skin involvement is fairly common, alopecia caused by sarcoidosis is not widely reported.[60–64] African-American women are most commonly affected[61]; however, reports with Caucasian women have also been described.[63,65] Although most cases of sarcoid alopecia have been found on the scalp, a case of nonscarring, sarcoid alopecia was described on the dorsal surfaces of the arms and legs.[66]

Clinically, sarcoid alopecia can present as plaques, erythema, scaling, folliculitis-like lesions and crusted regions. Ulcers and lesions resembling DLE are very common.[60–63] Scleroderma-like atrophy with exposure of underlying vasculature and frontal fibrosing-like alopecia have also been reported, demonstrating the wide variability of clinical presentations.[67,68]

A high incidence of systemic involvement has been noticed in patients presenting with sarcoid alopecia. There is report of a Native-American woman presenting with symptomatic hypercalcemia and scarring alopecia that was later found to have pulmonary involvement and diagnosed with sarcoidosis[64]; therefore, a thorough systemic checkup of these patients is of high importance.[61]

Trichoscopy will reveal perifollicular and follicular orange dots that correspond to naked granulomas on histopathology.[63] Additional findings include destruction of follicular units and miniaturized anagen follicles surrounded by epithelioid giant cells at the level of the isthmus.[60,63,65]

Treatment is challenging, showing little response to intralesional or systemic steroids and antimalarials.[61]

Psoriasis

Psoriasis is a chronic inflammatory skin condition that acts systemically and can cause hair loss at any affected site, including the scalp. Psoriatic alopecia of the scalp is usually nonscarring. It can present in regions of active disease or as a generalized telogen effluvium and can be due to systemic medications or even caused by the friction from applying local therapy.[69] AA-like patches have also been identified as a pattern of hair loss associated with psoriasis. Although the mechanism between alopecia and psoriasis has not been fully elucidated, experts believe that side effects of biologic treatments, especially with the tumor necrosis factor alpha inhibitors adalimumab and infliximab, are the main cause of AA in psoriasis patients.[70–73] Usually, their hair loss resolves after discontinuation of treatment.

On physical examination, psoriatic alopecia typically presents as pink, scaly patches with overlying alopecia. Patients with psoriasis have more dystrophic hairs, and the hair shaft diameter is narrower in lesional skin.[74] Thick white scales, red dots, globules, and twisted red loops are present on trichoscopy (Figure 6a).[75] Histologic features of psoriatic alopecia depend on the stage of disease. Early in the disease course, typical psoriatic features of the interfollicular epidermis can be seen as well as atrophy of sebaceous glands, increased catagen and telogen hairs, perifollicular lymphohistiocytic

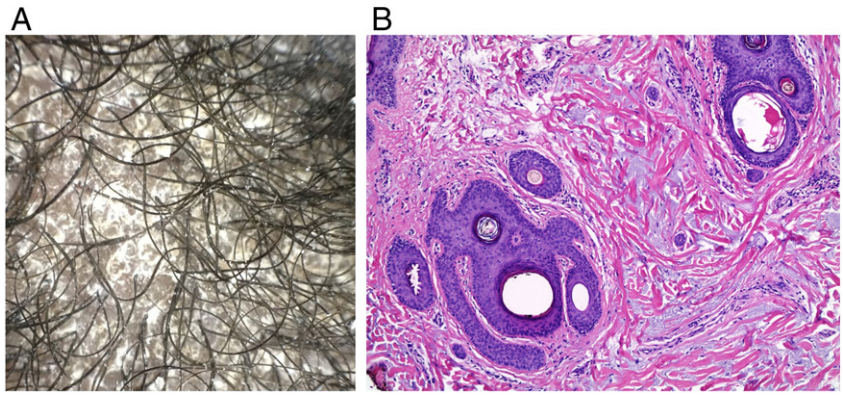

Fig. 6 **(a)** Scalp psoriasis shows thick plaques covered by white silvery scales (Handyscope, FotoFinder Systems, ×20). **(b)** On pathology, there is atrophy of the sebaceous glands that remain as mantle-like follicular structures (hematoxylin and eosin, ×20).

inflammation, and follicular miniaturization (Figure 6b).[69] Late histologic features may include chronic inflammation of the infundibular and isthmic regions, hair follicles with naked hair shafts, and destruction and fibrosis of the hair follicle.[69]

Malignancy

Alopecia associated with malignancy can be due to chemotherapy, radiation, paraneoplastic processes, or a direct manifestation of the malignancy itself.

Lymphoproliferative disorders

Most of the literature involving cutaneous lymphoma and hair loss consists of individual reports, highlighting the rarity of these conditions. Mycosis fungoides (MF) and Sezary syndrome (SS) are subtypes of cutaneous T-cell lymphomas (CTCL) that can present with alopecia.[30]

SS is a leukemic variant of CTCL characterized by generalized erythroderma, palmoplantar hyperkeratosis, pruritis, and total body hair loss.[76] Most commonly, CTCL in the form of MF or follicular MF presents with range of involvement from AA-like patches to alopecia universalis independent from or within overt MF lesions.[77,78] The histopathology shows follicular involvement of atypical infiltrate composed of CD4+ lymphocytes at the bulbar level and the isthmus (Figure 7). MF, presenting as a well-defined AA-like patch with an unusual infiltrate composed of CD8+ lymphocytes, suggests the need for biopsy in these cases.[79] One can distinguish AA from CTCL on trichoscopy, as CTCL reveals diffuse scaling with reduced follicular openings, broken hairs, short hairs, or keratotic filiform spicules compared with AA, which classically presents with black dots representing dystrophic hairs, yellow dots, and exclamation mark hairs.[30] Treatment for patchy MF includes topical corticosteroids, mechlorethamine, bexarotene, light therapy with narrowband ultraviolet B, and psoralen combined with UVA light treatment.[79]

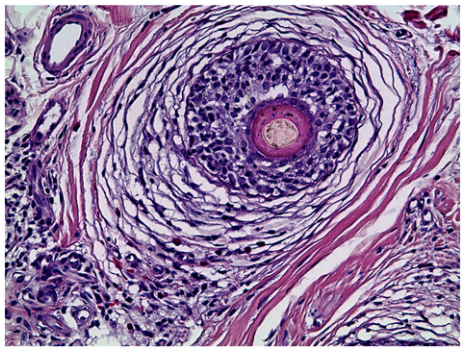

Fig. 7 Biopsy from alopecia-areata-like hairless patches associated with cutaneous T-cell lymphoma shows follicular epidermotropism, layered fibroplasia, and eosinophils (hematoxylin and eosin, ×10). The epidermotropic cells are CD4 positive.

Follicular mycosis fungoides (FMF), an aggressive form of MF characterized by atypical T-lymphocytes in the follicular epithelium, can present with scarring or nonscarring alopecia. In a study comparing FMF to conventional MF, 65% of patients with FMF had patchy alopecia, most commonly involving the face and eyebrows. FMF causing alopecia of the scalp was seen in a smaller subset of patients. All of these cases presented with cicatricial alopecia and large, papulonodular lesions.[80]

Alopecia neoplastica

Alopecia neoplastica is cutaneous metastasis resulting from underlying malignancy that displaces normal structures and hair follicles on the scalp. This type of alopecia neoplastica, or secondary alopecia neoplastica, has been distinguished from primary alopecia neoplastica, where malignancy originates on the scalp.[81] First described in 1949 in a patient with breast carcinoma metastases,[82] secondary alopecia neoplastica has now been reported as a result of many malignancies, including metastatic melanoma,[83] breast cancer,[84] primary pulmonary adenocarcinoma,[85] gastrointestinal cancers,[86] and placental trophoblastic carcinoma.[87]

These lesions can be cicatricial or noncicatricial and typically present on the scalp as patchy, erythematous, crusted, nodules, or plaques.[83,87,88] Histopathology of lesional skin is indicative of the underlying carcinoma; for example, desmoplastic melanoma, presenting as alopecia neoplastica, reveals atypical and nested epithelioid melanocytes in a sclerotic dermis with positive S100 expression.[83]

Postoperative alopecia

Postoperative alopecia (PA) is a cumulative outcome of several factors encompassing the time of surgery, including stress before surgery, head positioning during surgery, and lengthy operating times.[89] The main mechanism involves pressure-induced hypoxia similar to the mechanism of pressure ulcers, resulting in a circumscribed area of hair loss of the prominent bony area, typically the vertex or occiput.[30] PA has been described in prolonged orthopedic and gynecologic procedures, one case of vitreoretinal surgery, and even in oral surgery cases.[89,90] The onset can occur anytime within 3 days to 1 month after surgery and presents most commonly as well-circumscribed patches of hair loss (Figure 8). Hair regrowth, if possible, typically takes 1 to 4 months.[30]

Trichoscopy reveals broken hairs, cadaverized hairs, and black and yellow dots.[30] PA can be mistaken for AA and should be distinguished based on the absence of exclamation mark hairs. Biopsy shows catagen hairs without perivascular, periadnexal, or peribulbar inflammatory infiltrates. Apoptotic cells are present in the follicular epithelium.[91]

The prognosis for these patients exists on a spectrum from full recovery to permanent scarring, dependent on the amount

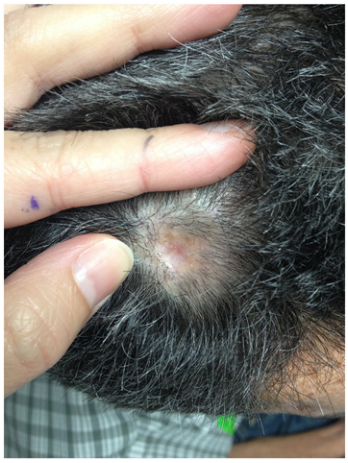

Fig. 8 Pressure-induced alopecia from tightly placed surgical sutures most likely inducing transitory ischemia. The hair in the patch regrew over time.

of time the scalp was deprived of oxygen.[92] Using a donut head rest, changing head positioning, and avoiding continuous compression are critical for avoiding PA in lengthy procedures necessitating general anesthesia.

Scalp infections

Leprosy

Scalp involvement in leprosy is rare. The scalp is considered immune from *Mycobacterium leprae,* probably due to its high local temperature.[93] Hair loss in mild to moderate leprosy is usually mild, because the deeper areas are not affected.[94] There are a few patients with alopecia secondary to leprae, where there are nontender plaques of alopecia with bullous and other areas with honey-colored crusts. There can also be changes on dermal and pain testing, and the patient may experience pruritus.[94,95]

Histopathology shows dermal involvement with lymphohistiocytic inflammatory infiltrate of multinucleate giant cells. Epithelioid granulomas are found surrounding the neurovascular plexus and skin appendages.[94]

With appropriate intervention for treating the underlying leprosy, complete resolution of alopecia is possible.[94]

Herpes infections

Herpes zoster (HZ) is a viral infection caused by reactivation of varicella-zoster virus from its latent state in the dorsal root ganglion. HZ has been associated with AA, and it is hypothesized that the Th1 lymphocyte predominance leads to loss of the hair follicle's immune privileges. One study followed 59,123 patients found to have HZ and discovered a higher prevalence of AA in herpes cases compared with controls at an odds ratio of 3.74. It is possible that stress associated with AA could increase the risk for developing HZ. Complete follicular destruction in severe lesions of HZ has also been demonstrated, possibly leading to alopecia,[96] but the mechanism is unknown.[97] Clinically, HZ on scalp may present as dermatomal folliculitis, AA-like patches, or scarring alopecia due to involvement of the dermal dendritic cells that participate in the tissue remodeling by the varicella-zoster virus (Figure 9a, b).[98,99]

Topical and intralesional therapy with steroids, together with the systemic antiviral treatment, leads to complete resolution of HZ-related AA.[98,99]

Tinea capitis

Tinea capitis is one of the most common dermatophyte infections affecting children. It is caused by either *Trichophyton* species, responsible for greater than 90% of cases in North America, or *Microsporum* species, which predominates in Europe. Tinea capitis causes nonscarring alopecia and can present with partial to complete patchy alopecia, a diffuse seborrheic dermatitis-like pattern with erythema and scaling, or with boggy, inflammatory nodules called kerions.[100] Cervical lymphadenopathy may also be present.

Trichoscopy may show many findings, including broken hairs, corkscrew hairs, comma hairs, barcode hairs, zigzag

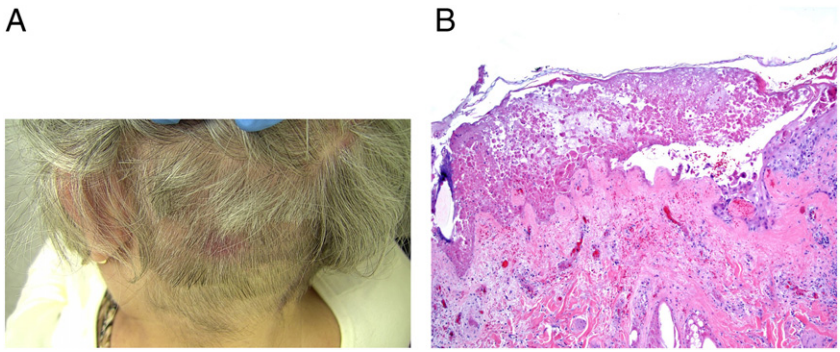

Fig. 9 **(a)** Herpes zoster infection of the scalp presenting as folliculitis. **(b)** Histopathology confirmed diagnosis of herpes zoster. There is reticular degeneration with multinucleated keratinocytes and necrotic keratinocytes. Note the follicular necrosis (hematoxylin and eosin, ×10).

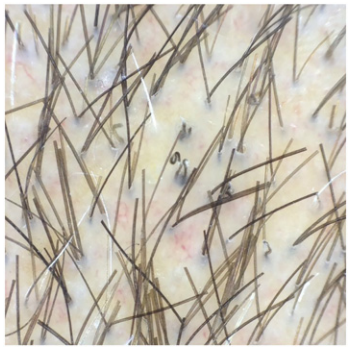

Fig. 10 Comma hair in a patient with inflammatory tinea capitis. The image is obtained from clinically noninvolved area the scalp (Handyscope, FotoFinder Systems, ×20).

hairs, and black dots (Figure 10). Usually, trichoscopy can lead to the correct diagnosis, bypassing the need for a biopsy. A biopsy from the comma hairs sent for horizontal sections has a higher diagnostic yield, as it allows the clinician to assess many follicles in a 4-mm punch specimen for arthrospores within the hair shafts. Special antifungal stains such as periodic acid–Schiff stain and Grocott's methenamine silver stain are useful aid for the diagnosis; however, the stains can be negative in up to half of the specimens from inflammatory tinea capitis.[101]

Terbinafine is the treatment of choice for tinea capitis caused by *Trichophyton* spp., whereas griseofulvin remains the first choice for tinea capitis caused by *Microsporum canis.*[102]

Syphilis

Syphilis is a sexually transmitted disease caused by *Treponema pallidum.* Multiple organs are affected, including the skin, where it can mimic many cutaneous conditions. The incidence of hair involvement can vary between 2.9% and 41.6%.[103,104] Syphilitic alopecia occurs in the setting of secondary syphilis and is nonscarring in nature. The mechanism entails antigens of the bacteria that attack hair follicles and promote a perivascular and perifollicular lymphohistiocytic dermal infiltrate with plasma cells.[104] The detection of spirochetes in the hair follicle has also been reported.[105,106] Syphilitic alopecia may be secondary or essential syphilitic alopecia, where alopecia is the only clinical sign of secondary infection. Essential syphilitic alopecia can present with a variety of patterns: "moth-eaten," diffused, and mixed, as well as alopecia of the eyebrows.[104,107,108] The "moth-eaten" pattern consists of small, ill-defined, localized alopecic patches in the parieto-occipital region.[104,105,107] Alopecia of the eyebrows displays the omnibus sign, which refers to loss of hair in the distal third of the eyebrows.[104] A diffuse, telogen-effluvium-like pattern of alopecia can present at any time in the course of the infection and can also be one of the only early clinical manifestations of syphilis.[109]

Trichoscopy shows reduced hair density, yellow dots, broken hairs, and increased portion of vellus hairs.[104,105,108] Histopathology is significant for decreased hair density with peri-infundibular inflammatory lymphocytic infiltrate deposition of IgG in the follicular basal membrane zone, C3 in follicular epithelium, and IgG and C3 in epidermal keratinocyte nuclei on are seen on immunofluorescence.[105]

Targeting syphilis with appropriate antibiotic therapy has proven to be effective for secondary syphilitic alopecia.[105]

Miscellaneous

Amyloidosis

Systemic amyloidosis is a disease in which there is abnormal, extracellular deposition of amyloid. It can be divided into three categories: systemic light chain amyloidosis is the most common amyloidosis, followed by secondary amyloidosis (AA) and then wild-type transthyretin cardiac amyloidosis (ATTRwt).[110] Amyloidosis has the potential to affect any organ.

The presence of alopecia in amyloidosis is rare. Diffuse nonscarring alopecias, as well as one cause of alopecia universalis, have been reported.[111] Trichoscopic findings include salmon-colored haloes around empty follicles and follicles containing terminal and vellus hairs, black dots, and broken hairs.

Histopathology reveals homogenized, avascular eosinophilic material, confirmed to be amyloid on Congo-red staining, surrounding each follicular unit. Interestingly, the amyloid deposition surrounding each follicle corresponds with the trichoscopic finding of the salmon-colored haloes.[111]

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