Symposium-Hair Disorders

What's new in cicatricial alopecia?

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ABSTRACT

Scalp hairs complete the body self-image and patients with alopecia suffer from overt disfiguration, leading to psychosocial embarrassment and significant lack of self-esteem. Hence an early diagnosis and an aggressive treatment in the case of active hair loss are crucial in the management of scarring alopecia. This review presents a comprehensive study of newer theories in aetiopathogenesis, evolving diagnostic modalities and a step ladder approach in management of primary cicatricial alopecia.

Key words: Cicatricial alopecia, primary cicatricial alopecia, secondary cicatricial alopecia, stable alopecia, unstable alopecia

INTRODUCTION

Cicatricial alopecias (CAs) or scarring alopecias are a group of uncommon inflammatory hair loss disorders, which are characterized by permanent destruction of hair follicles. Clinically there is loss of visible follicular ostia in the scarring area, with or without epidermal atrophy and histologically there is absence of pilosebaceous structures which are replaced by fibrous tracts.[1-5] CAs are classified as primary cicatricial alopecia (PCA), secondary cicatricial alopecia (SCA), and developmental/hereditary CA.

PCA is caused by destructive inflammation of the hair follicle. This destruction is attributed to various etiologies, which are predominantly autoimmune processes. In this article, we aim to review newer theories in aetiopathogenesis, recently described clinical patterns, and advances in management of the PCA.

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EPIDEMIOLOGY

Very few data on the epidemiology of CA is available in the published literature. One large retrospective study over 10 years showed the frequency of CA as 7.3% of all the hair loss cases. The majority of affected adults were females (2.6:1) and PCA was more common than SCA (4:1). Among causes of PCA, pseudopelade of Brocq (PPB) (40.6%) was most frequent followed by lichen planopilaris (LPP) (12.6%), and folliculitis decalvans (FD) (11.2%).[1]

In another retrospective study, 3.2% patients of hair disorders seen over 5 years had PCA, with majority cases characterized histopathologically by lymphocytic infiltrate (4:1). In this study, discoid lupus erythematosus (DLE) (33.9%) was the most common cause followed by PPB (24.1%) and LPP (22.3%).[2]

A recent questionnaire survey in UK, revealed incidence of PCA as 6.96 cases per 1000 new general dermatology referrals per year, equating to about 9.6 new cases per clinician per year.[3]

Classification

The causes of CA are broadly classified as primary, secondary, and hereditary or developmental defects.[4-6] In PCA, the hair follicles are the main targets of destructive inflammatory process resulting

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in irreversible hair loss from the affected site on scalp. The inflammatory cells targets and destroys the stem cells in the bulge area of hair follicles.[4] In SCA, the hair follicles are secondarily damaged as a result of more generalized destructive process within the skin, which ultimately destroys the hair follicle stem cell (HFSC)-based capacity for regeneration.[5] The causes of SCA are trauma (burns, radiation, traction), any infiltrative processes (morphoea, scleroderma, sarcoidosis, neoplasias), and infections (bacterial, fungal, viral, mycobacterial).[6]

Further, the working classification of PCA is based on the most representative pathological finding on scalp biopsies. PCAs are divided into subgroups depending upon the predominant inflammatory infiltrates, that is, lymphocytic, neutrophilic, and mixed [Table 1]. Chronic cutaneous lupus erythematosus (CCLE), LPP, classic PPB, central centrifugal cicatricial alopecia (CCCA), alopecia mucinosa (AM), and keratosis follicularis spinulosa decalvans (KFSD) are categorized under "lymphocytic" PCA. Frontal fibrosing alopecia (FFA) and Graham–Little–Piccardi (GLP) syndrome are considered as LPP variants. The neutrophilic PCA group comprises FD and dissecting cellulitis/folliculitis of scalp (perifolliculitis abscedens et suffodiens). Acne keloidalis nuchae (AK), acne necrotica (AN), and eruptive pustular dermatosis (EPD) are classified as "mixed" cell infiltrate PCA. In addition, nonspecific CA is defined as "idiopathic scarring with inconclusive clinical and histopathological findings". There have been debates whether this classification is satisfactory or not, however, it provides a practical and reasonable standard for clinical and basic studies thus has been widely used.[5-7]

Another classification proposed to facilitate determination of the most suitable surgical corrective therapies for CA, categorize it into "stable" and "unstable" type [Table 2].[8] "Stable" CAs are secondary to isolated events that cause permanent scarring in a hair-bearing region. Once corrected surgically, there is no need for constant vigilance. Whereas "unstable" cicatricial alopecias (UCAs) are secondary to disorders that have a tendency to progress and recur intermittently over the course of time. Therefore, prior to considering any surgical treatment, it is vital to identify the type of alopecia and also to confirm quiescence preferably for at least 1 year so that they can be successfully treated medically before scarring actually occurs.[8]

PATHOGENESIS

PCA is characterized by permanent destruction of hair follicles, progressive deposition of collagen, and is frequently associated with loss of sebaceous glands. The pathogenesis of PCA revolves mainly around the destruction of slow-cycling, pluripotent HFSCs.[9] These HFSCs are located in the 'bulge' region of hair follicle in outer root sheath (i.e., at the site of attachment of the arrector pili muscle to the outer root sheath). These stem cells are thought to produce secondary germ cells or transient amplifying cells that migrate in a bidirectional fashion, undergoing coordinated differentiation to restore and renew the upper follicle, including the sebaceous gland, and adjacent epidermis; and regrow the lower hair follicle during normal telogen–anagen cycling.[10]

But, HFSCs destruction alone cannot explain the full phenotypic profile seen in different PCA entities like erythema, epidermal atrophy, follicular plugging. Therefore, other pathogenic processes may account for such changes.[11]

The newer insights into the pathogenesis of PCA mainly involves the HFSCs destruction theories, impairment of self maintenance of HFSCs, alteration of lipid metabolism, neurogenic inflammation theory, environment, and genetic factors.[4,11-54]

Hair follicle stem cells destruction theory

This theory is based upon the observation of the peri-follicular inflammatory infiltrate relative to the two key structures of the hair follicle, the hair bulb (where the hair shaft is generated), and the hair bulge. In the prototypic reversible autoimmune hair loss disorder alopecia areata (AA), the inflammatory infiltrate is centered around the hair bulb; whereas in PCA, the infiltrate is mainly located around the bulge region and distal (noncycling) follicle. This marked difference in the intradermal location of the inflammatory infiltrate has major clinical consequences, that is, reversible versus permanent hair loss.[11-13]

Further, immuno-staining of keratin 15, (a recognized hair 'bulge' marker in humans) has shown to be diminished or absent from the bulge region in LPP and CCLE with predominantly dense peri-follicular inflammatory infiltrates, suggesting that the inflammatory process is destroying the HFSCs pool.[14,15]

Table 1: Clinical and histopathological characteristics of primary cicatricial alopecia

Clinical	Histopathology and immunoflourescence
Lymphocytic group	
CCLE: Erythematous scaly plaques with hyperkeratotic adherent follicular plugs, central atrophy, loss of follicular ostia, hypo- to depigmentation in the center with peripheral hyperpigmentation [Figure 1]. Patient complains of pruritus, burning, stinging sensation and scalp tenderness.[52,53]	**Histopathology:** Vacuolar interface alteration of follicular epithelium, scattering of dyskeratotic keratinocytes, variably dense periadnexal, perifollicular (upper portion), perivascular and interstitial lymphocytic infiltrate with dermal mucin, atrophy of sebaceous glands and follicular plugging. Epidermis may be atrophied with vacuolar interface changes. Concentric lamellar fibrosis around the follicle in end stages.[5,6,52-54] DIF: Deposits of immunoglobulin IgG or IgM and C3 in a granular or homogeneous band-like pattern at the dermal interface with the follicular epithelium and epidermis. Less commonly IgA deposits are seen.[5,6,52-54,87]
Lichen planopilaris **Classical LPP:** Multi-focal or central alopecic patches with peri-follicular, erythematous or violaceous papules and spinous follicular hyperkeratosis at hair-bearing margin, in active stage, whereas atrophic, depigmented scars mark the burnt out disease [Figures 2 and 3]. Patient complains of pruritus, burning, pain, scaling, and scalp tenderness[53,55] **Frontal fibrosing alopecia:** Seen in postmenopausal women, characterized by progressive symmetrical cicatricial alopecia in fronto-temporal area revealing uniform shiny pale-band of skin (1-8 cm), lacking follicular ostia. Immediate hairline shows perifollicular erythema and hyperkeratosis, eyebrows thinning or loss may be seen.[53,57] [Figures 5 and 6] **Graham-Little-Piccardi (GLP) syndrome:** Triad of progressive scarring scalp alopecia (patchy), non-scarring loss of pubic and axillary hair and widespread keratosis pilaris (KP)-like horny follicular papules.[53,58]	**Histopathology:** 'Active' stage reveals diagnostic features of follicular lymphocytic interface dermatitis with dense band like lymphocytes around the upper follicle and infundibulum obscuring DEJ, infundibular hyperkeratosis and hypergranulosis, cytoid bodies scattered along the BMZ, absent or atrophic sebaceous glands with or without pigmentary incontinence [Figure 4a and b]. In end-stage 'longitudinal tracts' of fibrosis at the site of former follicle with peri-follicular lamellar fibrosis and adjacent epidermal atrophy is seen.[2,53,55,56] **DIF:** 'Shaggy' or 'patchy' deposition of fibrinogen and clumped IgM or less commonly IgA and C3 deposits are seen along follicular BMZ.[53,55,56,87] Histopathology and DIF: Indistinguishable from classical scalp LPP.[53] Histopathology: Affected follicle shows horny plugging, destruction, dermal fibrosis and atrophic epidermis.[53]
Pseudopelade of Brocq: Multifocal, asymptomatic, skin colored patches of cicatricial alopecia [Figure 7] often with atrophy and no clinically apparent inflammation.[53,59]	**Histopathology:** Variably dense perifollicular lymphocytic infiltrate in early stage, followed by eccentric atrophy of follicle infundibular epithelium, concentric lamellar fibrosis around upper follicle and loss of sebaceous gland in later stage [Figure 8]. Elastin stains reveal dense elastic tissue cuffing a broad, fibrotic follicular tract in advanced disease, this differentiates it from other PCAs.[53,59]
Central centrifugal cicatricial alopecia: Encompasses hot-comb alopecia and follicular degeneration syndrome, characterized by slowly progressive scarring of vertex that spreads symmetrically and centrifugally, alopecia is incomplete with islands of unaffected hairs within scar area. Peri-follicular hyperpigmentation and polytrichia can be observed. Usually asymptomatic but unusual sensations, such as pins and needles, itch or tenderness may occur.[53,60]	**Histopathology:** Earliest feature is premature disintegration of the inner root sheath, resulting in outward migration of the hair shaft through the ORS at the level of the isthmus. Lamellar fibroplasias and lymphocytic inflammation surround the follicle at this level, resulting in follicular destruction and fibrous tract formation.[53,60]
Alopecia mucinosa: Characterized by follicular papules coalescing to form erythematous well-defined, indurated plaques with prominent follicular opening with loss of hairs. May be scarring or nonscarring, other morphologies like erythematous finely scaly tumors with patulous pores, noninflammed AA type, arciform alopecia, diffuse hair loss, scleroderma plaque like.[53,61]	**Histopathology:** Mucinous degeneration of the ORS and sebaceous glands. A perifollicular lymphocytic infiltrate often with eosinophils and histocytes is usually found.[53,61]
Keratosis follicularis spinulosa decalvans: Characterized by widespread erythematous follicular hyperkeratosis followed by punctate atrophy and cicatricial alopecia [Figure 9]. KP like lesions start from face in infancy and then spread to scalp, neck, trunk, and extremities. Less common features are photophobia, ocular abnormalities like corneal dystrophy, focal palmo-plantar keratoderma, atopy.[53,60]	**Histopathology:** Compact hyperkeratosis, hypergranulosis of the upper follicular epithelium with superficial intrafollicular and peri-follicular edema in early stage whereas in advanced stage there is concentric perifollicular, horizontal adventitial lamellar fibrosis and scarred follicular tracts.[53,60]
Neutrophilic group	
Folliculitis decalvans/tufted folliculitis: Destructive, suppurative folliculitis caused by *Staphylococcus aureus*, presents as painful/pruritic erythematous pin-point follicular pustules/papules with boggy swelling, folliculitis extends peripherally ultimately leading to crusting and scarring in the centre [Figure 10]. Tufts of hairs appear from dilated follicular opening giving 'doll's hair' appearance. Disease can be multi-focal.[62,63]	**Histopathology:** Acneiform dilatation initially with perifollicular neutrophilic inflammation around the upper follicle, which later develops into a more mixed inflammatory infiltrate of neutrophils, lymphocytes, and plasma cells. Follicular rupture ensues, resulting in foreign-body giant cell granuloma formation around exposed hair shaft fragments. In burnt out stage, follicular and adventitial fibrosis is seen.[62,63]

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Table 1: Contd...

Clinical	Histopathology and immunoflourescence
Dissecting cellulitis of scalp: Suppurative painful fluctuant nodules, abscesses, interconnecting sinuses, multifocal lesions eventually coalesce to give cerebriform appearance to scalp. Forms follicular occlusion triad/tetrad with acne conglobata, hidradenitis suppurativa and pilonidal sinus. Ultimately leads to CA with depressed, hypertrophic or keloidal scars.[53,64]	**Histopathology:** Infundibular acneiform distention with intrafollicular and perifollicular neutrophilic infiltration, abscess formation on follicular rupture composed of neutrophils, lymphocytes and plasma cells. In later stages abscess become partially lined by squamous epithelium forming sinus tracts.[53,64]
Mixed group	
Acne keloidalis nuchae: Pruritic/painful firm follicular papules and pustules coalescing to form large nodules and keloidal plaques seen mainly on occipital scalp and nape of neck.[65]	**Histopathology:** Early disease is characterized by perifollicular and intrafollicular lymphoplasmacytic infiltrate more pronounced at the level of sebaceous glands, in advanced stage complete follicular destruction occurs with loss of sebaceous glands and dermal fibrosis.[65]
Acne necrotica varioliformis: Characterized by crops of pruritic, tender, erythematous, umblicated papulo-pustules that undergo central necrosis with resultant scar formation, sites involved are anterior scalp, eyebrows, nose, neck, and chest.[53]	**Histopathology:** In early disease there is dense perivascular and perifollicular lymphocytic infiltrate with prominent sub-epidermal edema. Necrosis of individual keratinocyte is seen initially and is followed by confluent necrosis of the central follicle and interfollicular epidermis.[53]
Erosive pustular dermatosis: Characterized by chronic relapsing amicrobial pustular dermatoses, progresses to form well-demarcated boggy swelling, which is easily deroofed to reveal beefy red, exudative erosions.[66]	**Histopathology:** Nonspecific, variable degree of epidermal erosions, atrophy, acanthosis, parakeratosis, and sub-corneal pustules. The dermis shows mixed chronic inflammatory infiltrate with reduced or absent hair follicles.[66]

Table 2: Stable and unstable cicatricial alopecia

Stable cicatricial alopecia	Unstable cicatricial alopecia
Trauma	**Lymphocytic**
Burns	Cutaneous discoid lupus erythematosus
Radiation-induced alopecia	Classic lichen planopilaris
Prior hair transplantation	Frontal fibrosing alopecia
Prior rhytidectomies and brow lifts	Graham-Little syndrome
Traction alopecia	Classic pseudopelade of Brocq
Trichotillomania	Alopecia mucinosa
Pressure alopecia	Keratosis follicularis spinulosa decalvans
Congenital	**Neutrophilic**
Aplasia cutis congenita	Folliculitis decalvans
	Dissecting cellulitis of scalp
Lymphocytic	**Congenital**
Central centrifugal cicatricial alopecia	Conradi-Hunermann chondrodysplasia punctata
	Incontinentia pigmenti
	Ankyloblepharon
	Others
	Acne keloidalis nuchae; acne necrotica
	Erosive pustular dermatosis
	Metastatic/primary neoplasm
	GVHD
	Infections

Similarly, other studies showed that the bulge region, marked by the biomarkers such as keratin-15 and -19 and CD200, is preferentially affected and replaced by fibrotic tissue in PCA leading to permanent hair loss.[16,17] Recent studies reported some cell populations marked by MTS24,[18] Lrig1,[19] Nestin,[20] Lgr5,[21] and Lgr6[22] are also capable of reconstituting hair follicles, suggesting that these cells are endowed with some stem cell characteristics. But the inflammation and subsequent fibrosis in PCA affect most of these cell populations also, except Lgr5 expressing cells.[4]

Collapse of hair follicle immune privilege

Hair follicles provide major portal for entry of microbial agents but in immuno-competent individuals the clinical consequences of such invasions are rare, this is because of anti-infection defense mechanisms like intraepithelial T-cells, Langerhans cells, perifollicular mast cells, macrophages, and antimicrobial peptides (human β2-defensin, psoriasin, cathelicidin, and RNAse7). These substances together with various chemokines and proinflammatory molecules can cause massive inflammation, which can also breach the follicular epithelium. But the hair follicle has established a state of immuno-suppression known as 'immune privilege' in its bulb and bulge region. This is done by the expression of potent endogenous immuno-suppressants like TGF-β1 and 2 (secretes macrophage inhibitory factor), α-MSH in hair follicular epithelium and low or absent expression of MHC class I and II molecules around the bulb and bulge.[11]

'Hair follicle immune privilege collapse' is thus an attractive theory to explain the exposure of HFSCs to

immune-mediated attack in PCA. The data supporting this show the immune reactivity of MHC class I, β2-microblobulin, and MHC class II, is upregulated in the hair 'bulge' region of lesional skin, compared with uninvolved skin, in different PCA entities.[23]

Cytotoxic cell mediated hair follicle damage and proinflammatory response leading to PCA

This hypothesis is based upon the inflammatory infiltrate observed in the scalp biopsies of CCLE, LPP, and FD. In scarred areas of CCLE, there is upregulation of γδ-T-lymphocytes with increased expression of chemokine 4, co-localization of skin homing marker cutaneous lymphocyte antigen (CLA) with the cytotoxic marker granzyme B leading to direct cytotoxic tissue damage.[4,11] Various proinflammatory cytokines like INF-γ, TNF-α, IL-2 are upregulated in the lesional skin of LPP, CCLE, and FD, leading to direct tissue damage and hence scarring.[4,11]

Increased apoptosis in PCA

Apoptotic keratinocytes are commonly observed during the histological assessment of PCA, suggesting a potential role of apoptosis in these disorders. In CCLE, apoptosis is increased in the hair follicle epidermis with the upregulation of epithelial proliferation marker Ki-67 and the tumor suppressor gene p53. The p53 direct the damaged cells into apoptosis.[24,25] Also, the expression of the constitutive apoptosis inhibitor Bcl-2 is reduced in CCLE, further predisposing to apoptosis-related tissue injury.[23] Peri-follicular FASL+ infiltrate is thought to play a key role in the follicular destruction commonly seen in CCLE through inappropriate apoptosis induction.[24,26]

Lipid metabolism dysregulation in PCA pathogenesis

With an insufficient evidence, this hypothesis is based upon the observation of spontaneous mutation, in widely studied mouse model for PCA.[27] It states that defect in stearoyl-CoA desaturase 1 (required for sebaceous gland fatty acid composition) results in sebaceous glands atrophy and abnormal gland secretions, which in turn lead to delayed inner root sheath disintegration, retrograde hair shaft growth and penetration of the bulb, with resulting foreign body reaction and eventual destruction of the hair follicle.[27,28] This supports the idea that inflammation in scarring alopecia is a secondary event resulting from a primary defect in the pilosebaceous unit.[29]

Another evidence supporting this hypothesis, is a recent study on decreased expression of genes for peroxisome proliferator-activated receptor γ (PPARγ) (required for lipid metabolism) and peroxisome biogenesis which triggers the pathogenesis of LPP.[30] The study states that decrease in expression of these genes led to progressive loss of peroxisomes, accumulation of proinflammatory lipids, and infiltration of inflammatory cells around the pilosebaceous structures followed by destruction of the complete pilosebaceous unit.[30] Based upon this theory, the beneficial role of PPARγ agonist in LPP has been described.[31] (Detailed more under "Management" section.)

Impaired self-maintenance of hair follicle stem cells cause hair loss

An experimental study, reported the loss of interaction between Col17a1 and HFSCs (which impairs the self-renewal capacity of stem cells) resulting in permanent hair loss in mice. It also demonstrates the change in microenvironment, including decreased extracellular matrix expression, causing scarring alopecia. Thus, it is possible that impaired self-maintenance or loss of self-regenerative potential due to environmental changes may also be responsible for PCA development.[32]

Neurogenic theory

It explains the possible role of psycho-emotional stress in PCA. The substance P (SP) a neuropeptide molecule, which is increased in the state of psycho-emotional stress, is an inducer of mast-cell dependent neurogenic inflammation. This results in dense peri-follicular inflammatory cell infiltrates (especially around the bulge), accumulation and degranulation of peri-follicular mast cells, increased hair follicular keratinocyte apoptosis and reduced hair matrix keratinocyte proliferation, which is followed by premature entry of hair follicle into catagen.[33-35]

SP when added to the cultures of human hair follicles in anagen phase, upregulates the expression of MHC class I molecule and β_2 microglobulin in peri-follicular region, leading to collapse of immune privilege and thus giving way to HFSCs destruction.[36]

SP is also a known fibroblast growth factor (FGF), thus promoting fibrosis and scar formation after inflammatory damage.[37]

Environmental factors contributing PCA

Various environmental triggering factors for PCA are proposed like infections, trauma, drugs, etc. The role of *Staphylococcus aureus* in FD is well known, the

abnormal host immune responses to the bacterial antigen are responsible for the intense inflammation and scarring alopecia in the disease.[5,6]

CCCA,[38] FD,[39] AK,[40] and erosive pustular dermatosis of scalp[5,6] are associated with traumatic hair care practices.

Drug therapies are also implicated in PCAs. Graham–Little syndrome has been reported following hepatitis B vaccination,[41] AK has been associated with anticonvulsant and ciclosporin therapy,[42,43] and drug-induced cases of AM,[44] CCLE[45] have been described. Similarly, occurrence of LPP is reported after ingestion of gold,[46] hepatitis B vaccination[41] and hepatitis C infection.[47]

Genetic factors related to PCA

Several reports of the familial PCA cases in PPB, FD, GLP syndrome, and KFSD suggested the existence of genetic factors.[48-51] X-linked KFSD represent genetic scarring alopecia, which is caused by a missense mutation in the *MBTSP2* gene.[51] Thus, genetic factors are likely to underline the pathogenesis of several PCA entities in some form, either by predisposing an individual to a certain disorder or through a direct genetic effect, causing the condition. Further genetic studies of the families affected are required to identify the genes associated.

CLINICAL FEATURES

The characteristic clinical features of each type of PCA are enumerated in Table 1. A new entity described is 'cicatricial marginal alopecia' (CMA).[67] In this condition, the patient presents with an unusual clinical pattern of alopecia with severe loss of hairs from a wide band-like area on the margins of scalp. The site of involvement most commonly is occipital scalp (40% cases), other being temporal area. On close examination of scalp, there is no clinical appreciable scarring, atrophy, or erythema. Clinical differential diagnosis of CMA includes AA and tractional alopecia (late stages). But there is no history of hair care practices leading to tractional hair loss. Histologically, CMA reveals replacement of hair follicle by columns of fibrous tissue at or below the level of isthmus, with retention of sebaceous glands. This pattern of fibrosis was consistent with scarring alopecia.[67]

DIAGNOSIS

Dermoscopy/Trichoscopy

Dermatoscope is a convenient instrument that aids in diagnosis of skin and scalp lesion. It works on the principal of light reflected by the specimens. This is done by both hand-held dermatoscope using polarized light as well as with video dermatoscopy, which ensures 1000 times magnification.[68,69]

Dermoscopy of PCA reveals absence of follicular ostia in 100% cases even if it is not evident clinically, other findings suggestive of PCAs are tufted hairs, follicular hyperkeratosis, pili torti, and pink-white appearance.[68,70,71] Trichoscopy also helps clinicians assessing PCA disease activity, for example, "follicular red dots", erythematous polycyclic, concentric structures regularly distributed in and around the follicular ostia, are suggestive of active lupus erythematosus of the scalp.[70,71] A recent review, gives an algorithmic description of trichoscopic features of CA and non-CA [Table 3].[71] This further emphasizes that trichoscopy provides the excellent first-line, noninvasive method for assessing scalp and hair characteristics in clinics giving important clues to diagnosis.

Reflectance confocal microscopy

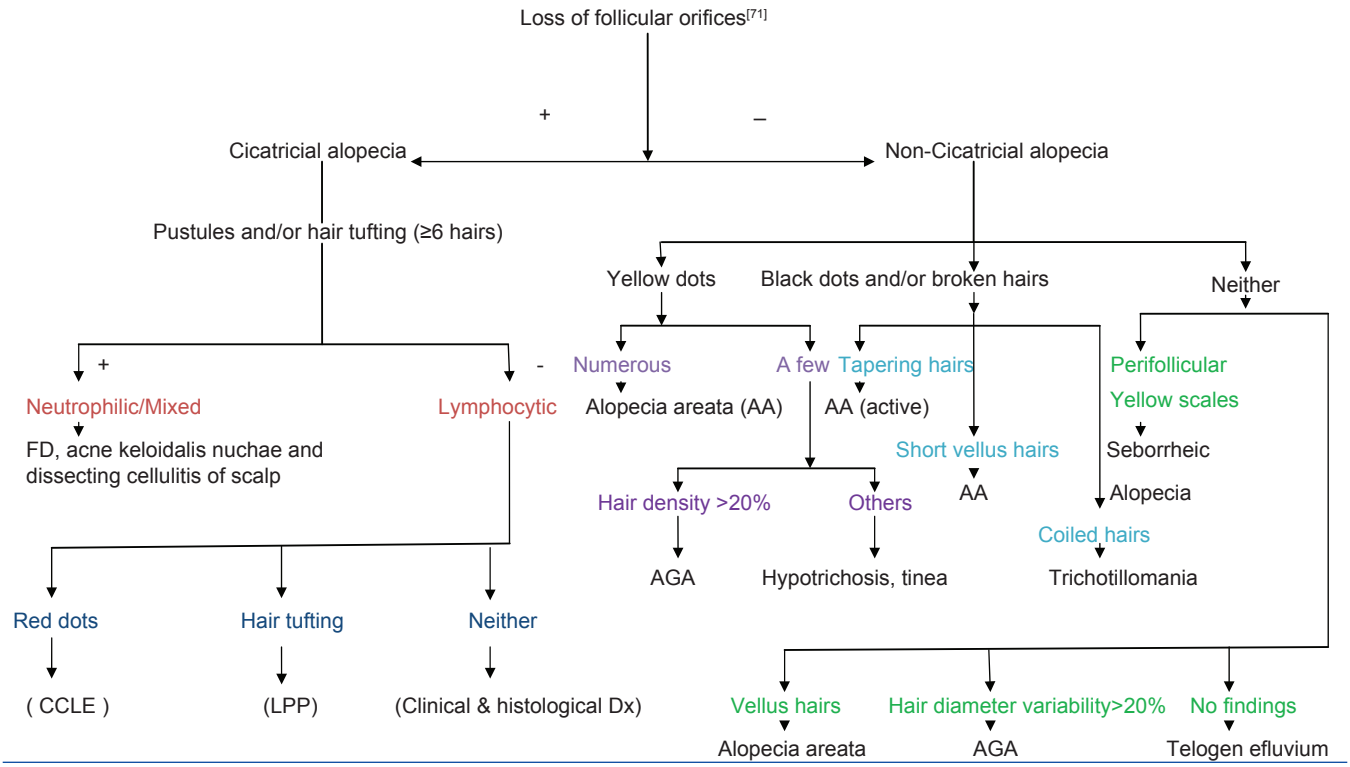
Reflectance Confocal Microscopy (RCM) is an *in vivo*, noninvasive, repeatable technique of real-time, en-face microscopic imaging of the superficial layers of the skin down to the superficial reticular dermis, with resolution at cellular level close to conventional histopathology.[72-78]

RCM has been used for the evaluation of several inflammatory skin conditions, such as acute contact dermatitis,[73] psoriasis,[74] nonscarring alopecia,[75,76] and in assessment of CCLE.[77]

A study evaluating RCM features of PCA (mainly LPP and CCLE) reveals epidermal disarray, spongiosis, exocytosis of inflammatory cells in the epidermis, interface dermatitis, peri- and intraadnexal infiltration of inflammatory cells, dilated vessels in the dermis, dermal infiltration of inflammatory cells, melanophages, and dermal sclerosis as features of PCA. It also differentiated LPP and CCLE based upon RCM features and has shown strong reduction to disappearance of inflammatory cells with treatment.[78]

Thus, RCM is a high-resolution imaging technique

Table 3: Algorithm for trichoscopic diagnosis of hair loss diseases



that may be helpful in the diagnosis and follow-up of scarring alopecia. It may also help in choosing the most appropriate biopsy site for more informative histology.

Histopathology

Histopathology of scalp is an essential tool in distinguishing CA from non-CA and in diagnosing the different PCA depending upon the inflammatory infiltrate. For an accurate histopathological diagnosis of PCA, multiple biopsy samples are obtained from active sites and carefully sectioned both vertically and transversely.[2] Unlike in other skin diseases, the information obtained by vertical sections is limited in hair disorders. Transverse sections enable both qualitative (e.g., inflammatory change, fibrosis) and quantitative (e.g., hair follicle numbers, size, phase of hair cycle) examination of scalp biopsy samples.[79]

Recently, the "HoVert" technique, a novel processing technique that produces transverse (horizontal) and vertical sections from a single biopsy has been described. This overcomes the limitation of multiple scalp biopsies [Figure 11].[80]

Based upon the histopathological picture, the CAs are divided mainly into lymphocyte-mediated primary cicatricial alopecia (LMPCA), neutophil-mediated primary cicatricial alopecia (NMPCA), and mixed CA [Table 1].[7,81,82] The diseases clubbed under LMPCA (LPP, FFA, DLE, CCCA, PPB) are typified by a lymphocyte rich infiltrate in early stages and with variable but limited fibrosis concentrated in the perifollicular adventitial unit in later stages. In contrast, in NMPCA group (FD, TF), there is a neutrophil-rich infiltrate in early disease, a mixed infiltrate in later disease, and marked scarring that extends beyond the peri-follicular dermis and extensively involves the reticular (inter-follicular) dermis.[103,104] In mixed CA group entities like AKN, AN, EPD inflammatory infiltrate is mixed lympho-plasmacytic or neutrophilic.[7]

The differentiation between the LMPCA and NMPCA group is easier in early stages of inflammation, whereas in later stages the differences in all PCAs as well as late stage of non-CA are subtle. To solve this query one study suggested, that the presence of plasma cells within the infiltrate in a given biopsy serve as a clue to a diagnosis of NMPCA,[83] whereas another points that the presence of 'compound follicle' (complex follicular unit fused at the level of the infundibulum) are a clue to diagnosis CA.[84] In yet another study, the number of 'compound follicles' was suggested to distinguish between LMPCA

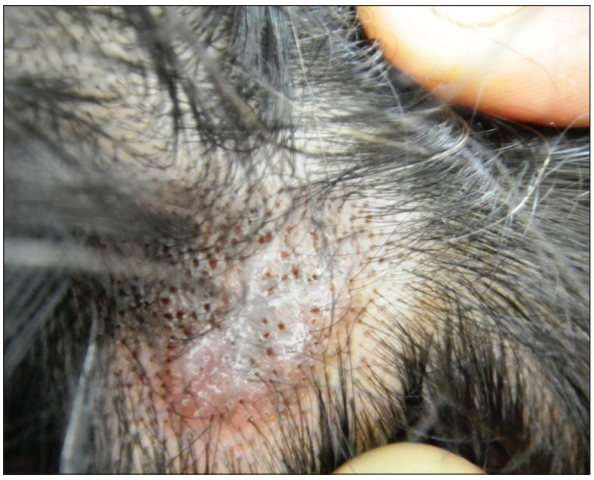


Figure 1: Scalp DLE, showing erythematous atrophic plaque with central depigmentation, dilated follicular orifices, follicular plugging, and loss of follicular ostia

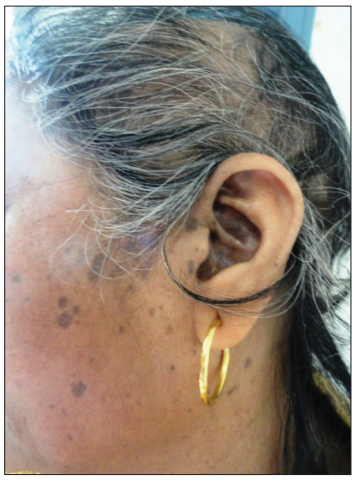


Figure 3: Violaceous pigmented spots of LP on face along with scarring alopecia

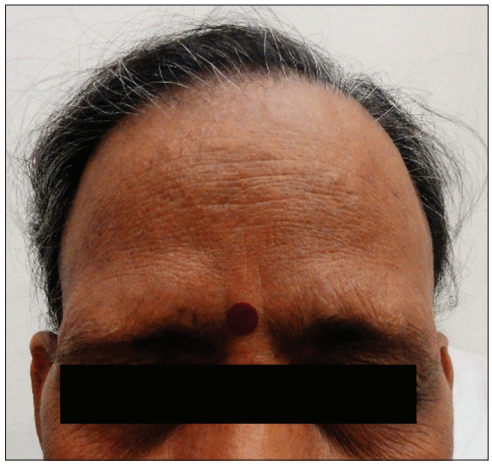


Figure 5: Wide band of bald frontal scalp with bilateral symmetrical thinning of lateral eyebrows in postmenopausal women suffering from FFA

and NMPCA with fewer (two or three) in the former and more melded follicles (four, five or more) in the latter.[85]

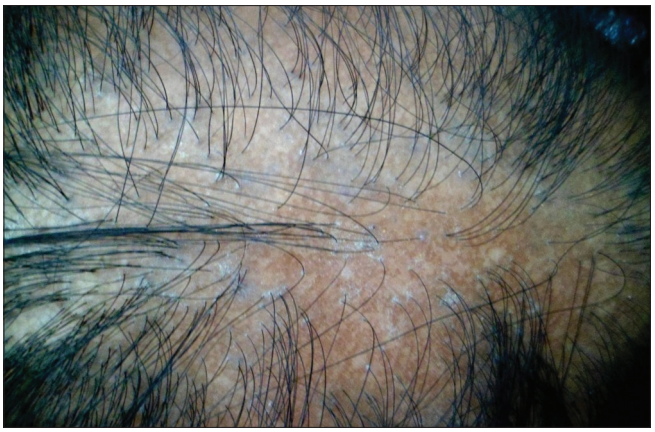


Figure 2: Patch of LPP, showing violaceous, peri-follicular papules in the periphery and loss of follicular ostia, dyspigmentation in the center

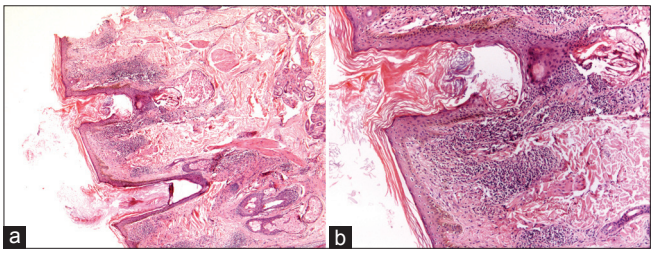


Figure 4: (a) Microphotograph showing hyperkeratosis with peri-follicular inflammation and atrophy of sebaceous unit in a case of LPP (H and E, ×20), (b) Heavy lymphocytic infiltrate around dermoepidermal junction and peri-follicular area (H and E, ×40)

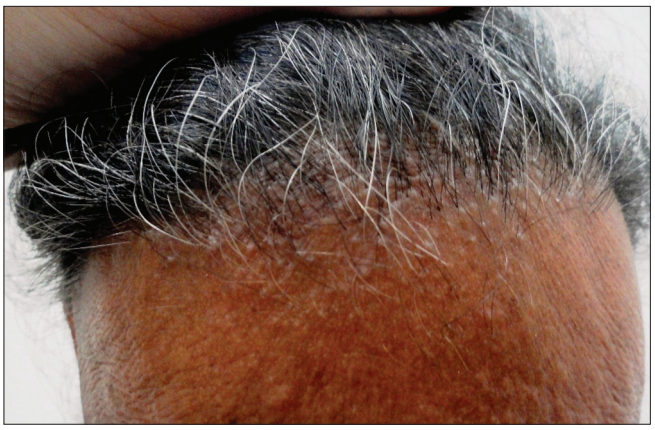


Figure 6: Closer view of the frontal scalp of the same patient suffering from FFA, showing perifollicular erythematous papules at the hair margin (in the active stage of disease)

In a recent study, 'eyes' or 'goggles' patterns of fibrosis observed at lower power at the level of infundibulum has been considered to be suggestive of LMPCA.[86]

Direct immunofluorescence study

It is an important diagnostic tool differentiating between PCA due to LPP or CCLE. In CCLE, it shows granular deposits of immunoglobulin (IgG) and complement (C3)

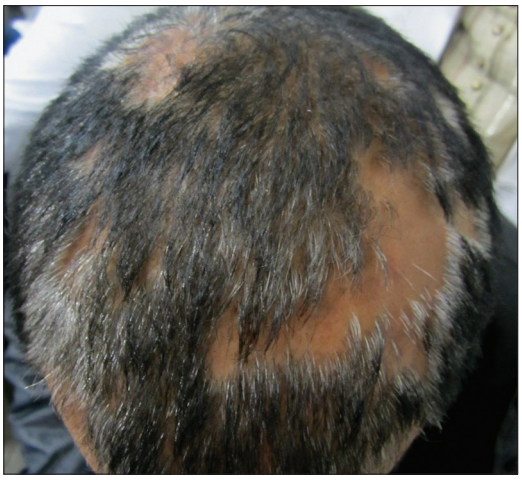


Figure 7: Multifocal, skin-colored plaques of pseudopelade of Brocq with complete loss of follicular ostia and no signs of inflammation

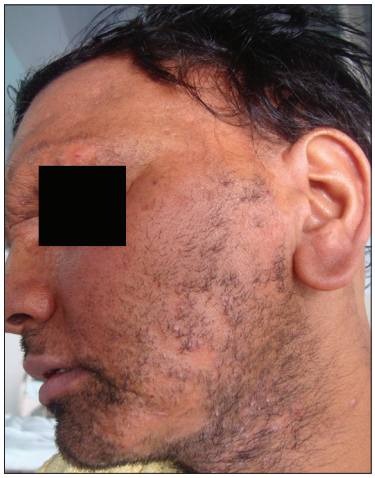


Figure 9: Multiple scarring alopecia areas seen in beard and eyebrows in a patient of KFSD

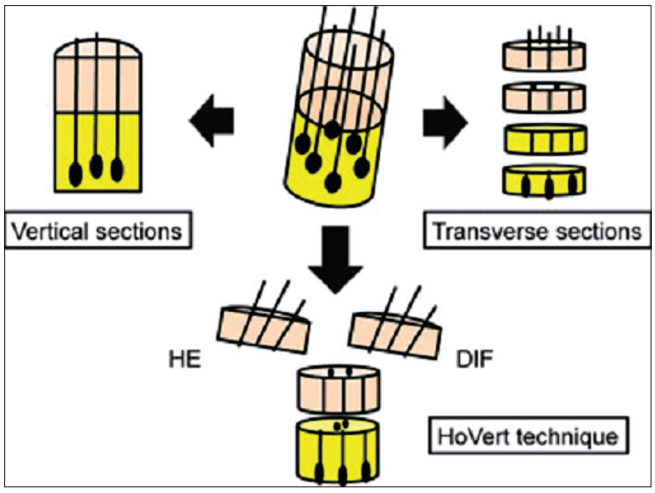


Figure 11: 'Hovert' technique

at the dermoepidermal junction, while in LPP there are globular deposits of IgM adjacent to the hair follicles or at the dermoepidermal junction [Table 1].[52-56,87]

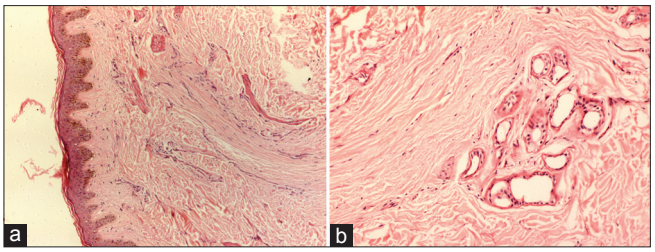


Figure 8: (a and b) Microphotograph showing thinned out epidermis with total loss of hair follicles, replaced by collagen in a case of PPB (H and E, ×20)

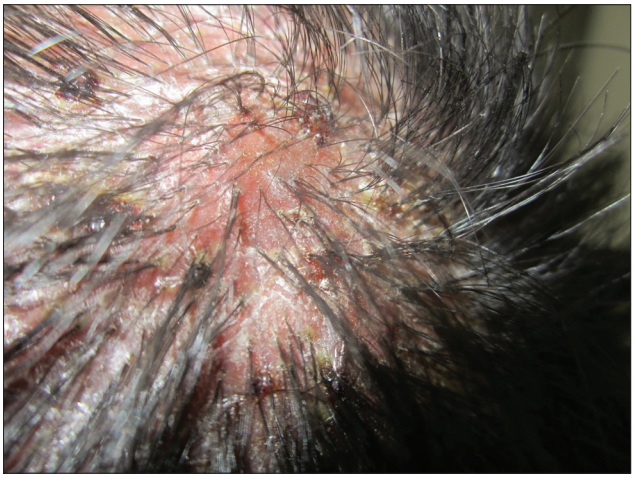


Figure 10: Folliculitis Decalvans showing scarred scalp with yellowish, crusted pustules at the periphery with matted and tufted hairs in the centre of plaque

Microarray analysis

Microarray analysis represents the global gene expression profile, as a diagnostic tool for clinically or pathologically indistinguishable PCA. Recently, a report of microarray analysis generated from total RNA isolates from active lesions of LPP and PPB, distinguished the two conditions, which were thought to be related.[88] However, further studies in this field may elucidates the genetic and molecular markers of various PCAs.

MANAGEMENT

PCA provides both the diagnostic and therapeutic dilemma to the treating dermatologist. The aim of treatment currently focuses the reduction of symptoms and to reduce or stop the progression of the disease. A general rule followed is to treat LMPCA with immunosuppression and NMPCA with antimicrobials or dapsone.[60] The step ladder treatment of PCA is given in Table 4.

Newer in treatment of LPP is the use of PPARγ agonists based upon the recent theory in pathogenesis suggesting

Table 4: Therapeutics in primary cicatricial alopecia

Clinical disease entity	Therapeutics step-ladder[53,60]
DLE	**First line** Class I or II potent topical corticosteroids I/L Triamcinolone acetonide injections (10 mg/ml, max 2 ml, every 4-6 weeks)[53] Results are assessed till 8 weeks, if no response shift to next level[53] **Second line** Antimalarials (Hydroxychloroquine 200-400 mg/day, effective in early progressive disease, clinical effect in 4-8 weeks, continued till 3-6 months)[53,60,89-91] Oral corticosteroids (1 mg/kg, for initial actively progressing disease, tapered over 8 weeks)[53,60,89,90,92] Retinoids (acitretin and Isotretinoin, 10-40 mg/day)[53,60,89,90,93] **Third line** Thalidomide,[94,95] topical immunomodulators (0.1% tacrolimus[96-98] and 1% pimecrolimus[99,100]), oral vitamin E,[101] oral gold,[102] dapsone,[103] mycophenolate mofetil,[104] methotrexate,[105,106] azathioprine,[60] clofazamine,[60] systemic or intralesional INFα2,[107,108] monoclonal anti-CD4 antibodies,[109] topical 5-FU,[110] topical tazarotene,[111] imiquimod.[112]
LPP	**First line** Potent topical corticosteriods[113,114] I/L Triamcinolone acetonide[113,114] **Second line** Oral corticosteroids[53,60] Oral cyclosporine (4-5 mg/kg for 4-6 months)[113,115-16] Topical cyclosporine (oily solution, applied twice daily for initial 3 months and once daily for further 3 months)[113,117] Oral tetracycline[114] **Third line** Oral retinoids (acitretin)[53,60] Antimalarials[2,53,60] Mycophenolate mofetil (500 mg twice daily)[118] Others: Thalidomide,[119,120] griseofulvin,[121] low molecular weight heparin (s/c injections 3 mg once weekly),[122] exicmer laser[123] **Newer therapies** PPARγ agonist like thiozolidinediones[31]
FFA	Intralesional triamcinolone acetonide[124] Finasteride (2.5 mg, OD)[125] Oral corticosteroids[126] Antimalarials[60,126] Topical corticosteroids with topical minoxidil[127] Oral retinoids[128]
GLP	Topical and intralesional corticosteroids[129] Oral ciclosporin[130] Systemic corticosteroids[42,131] Topical tacrolimus[132]
PPB	Potent topical corticosteroids(±)[53,60]
Alopecia mucinosa	**First line** Potent topical corticosteriods[60] **Second line** I/L triamcinolone[53,60] Minocycline[133,134] Topical±Oral indomethacin[135] Dapsone[136,137] **Third line** Systemic steroids,[138] isotretinoin,[139,140] antimalarials,[53,60] PUVA,[141] interferon α-2b+Interferon γ,[142] superficial X-rays[53,60]
KFSD	Potent topical corticosteroids±keratolytics[143] Oral antibiotics (depending on c/s)[144] Dapsone[145] Oral retinoids[146] Laser epilation[147]
FD	**First line:** Oral±topical antibiotics[148,149] **Second line:** Oral rifampicin (300 mg BD)+oral clindamycin (300 mg BD)[62,150,151] Rifampicin+ (doxycycline/ciprofloxacin/clarithromycin)[62,150,151] Oral rifampicin+topical antibiotics[152]

Contd...

Table 4: Contd...

Clinical disease entity	Therapeutics step-ladder
	Third line Oral fusidic acid[53,60,153] Oral zinc[154] Dapsone[155] Oral cyclosporine[156] Excision,[62] laser,[157] radiotherapy[158] i/m Human immunoglobulin (12.38 mg/kg, monthly)[159]
Dissecting cellulitis of scalp	**First line** Oral isotretinoin[64,160,161] Oral isotretinoin+i/l triamcinolone acetonide[162] **Second line** Oral antibiotics+topical antibiotics/topical retinoids[163,164] Aspiration and i/l triamcinolone acetonide[60,64] **Third line** Low dose corticosteroids[163] Colchicine[60,64] Dapsone[60,64] Excision and skin grafting[165,166] Lasers and radiotherapy[167,168,169]
Acne keloidalis nuchae[82,228]	**First line** Potent topical steroids[65,170] Oral antibiotics+topical steroids/intralesional triamcinolone[65,170] **Second line** Surgical excision[65,170,171] CO_2 laser[170] Diode laser hair epilation[172] **Third line** Radiotherapy[170] Isotretinoin[170]
Acne necrotica varioliformis	Oral antibiotics[53,6083] Oral isotretinoin[173] I/L triamcinolone[53,60]
Erosive pustular dermatosis of scalp	Topical corticosteroids[66] Topical immunomodulators[66,174] Calcipotriol cream[175] Oral Isotretinoin[66]

the role of abnormal functioning PPARγ receptor as an initial trigger of inflammation in LPP.[30,31] In a case report, pioglitazone Hcl (PPARγ agonist) 15 mg once daily was given to a patient of unstable LPP, in whom various treatment modalities including oral corticosteriods, antimalarials, MMF, failed to control the disease activity. With 8 months of pioglitazone, there were reportedly decrease in signs and symptoms along with reduction in inflammatory infiltrate in scalp biopsy.[31]

Thiazolidinediones or glitazones act by increasing activity of the nuclear receptor PPARγ and have antiinflammatory, antiproliferative, immunomodulatory effects, which includes downregulation of proinflammatory nuclear transcription factors, proteolytic enzymes, and interleukins. Thus, it helps in lipid biogenesis in pilosebaceous units and is antiinflammatory, immunomodulatory in active stage of LPP.[176,177]

Surgical treatment of scarring alopecia includes hair transplantation, scalp reduction or alopecia reduction surgeries, tissue expansion, and flap surgeries.[8,178,179] Decision for surgical treatment is based upon the stability of the CA, because best results can only be obtained in stable cicatricial alopecia cases.[8] Depending upon the duration of stable disease, some authors recommend the surgical therapies after at least 1 year of quiescence,[8] whereas others state that this should be after 2 years of disease-free interval.[60] The other factors that require consideration before planning the surgical treatment for CA includes vigilance regarding possible evolution of future androgenetic alopecia in the patient under treatment, availability of donor hairs and donor–recipient area ratio, vascular supply to the recipient area, scalp laxity, patient's healing characteristics, and location of the subsequent scars.[8]

The surgical treatment is individualized depending upon the above mentioned factors but in general surgical excision or alopecia reduction surgeries are

preferred for both unstable and stable CA. The success of hair transplantation in CA is limited by various reasons like disproportionate donor–recipient area ratio, decreased survival of hair grafts in scarred area due to compromised vascular supply and relapses of the disease process leading to new areas of scarring alopecia. However, in view of recent platelet rich plasma therapies to provide growth factors for grafted hairs and to increase graft survival at recipient site, hair transplantation will provide better results in stable CA.

CONCLUSION

PCA is 'trichology emergency' situation, in which lack of prompt and early treatment will lead to the inevitable loss of hair follicles along with permanent scarring. Newer pathogenesis has given the platform for development of emerging treatment modalities. But still a great deal of research is required in this field, may be developing viable stem cell therapies or bioengineered human hair follicles are the answers to it in future.

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