Alopecia in Autoimmune Blistering Diseases: A Systematic Review of Pathogenesis and Clinical Features of Disease

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Keywords

Alopecia · Autoimmune blistering diseases · Pemphigus · Pemphigoid · Trichoscopy · Hair loss · Scalp

Abstract

Background: Autoimmune blistering diseases (AIBD) are characterised by the body's production of autoantibodies against structural proteins in the epidermis and/or the basement membrane on cutaneous and mucosal surfaces. Alopecia is a complication of AIBD that has generally been overlooked in patients with severe blistering diseases because it is regarded as a cosmetic issue. Yet recent research into quality of life tools has found that stigmatisation by appearance plays a significant role in blistering diseases. **Aim:** To review the current literature detailing the pathogenesis and clinical presentations of alopecia in AIBD patients. **Method:** We searched Medline, PubMed and EMBASE electronic databases up to September 2018, for empirical human and animal studies. **Results:** Only 36 human studies including 223 patients (190 pemphigus, 25 pemphigoid, 5 epidermolysis bullosa acquisita, 2 dermatitis herpetiformis and 1 linear IgA disease) detailed demographic and clinical manifestations of alopecia. A range of hair evaluation methods was demon-

strated to reach alopecia diagnosis. Furthermore, with no universal validated scoring system for alopecia severity, alopecia patterns have been summarised. **Conclusion:** Previous randomised trials have not highlighted alopecia as an important outcome of AIBD, so epidemiological evaluation of the available literature has been helpful in summarising trends between existing studies and demonstrating inconsistencies.

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Introduction

Alopecia is a broad term describing patterns of hair loss and can be a complication of autoimmune blistering diseases (AIBD) such as pemphigus vulgaris (PV) and bullous pemphigoid (BP) [1]. These skin conditions are typically characterised by autoantibodies against structural proteins in the epidermis and/or the basement membrane on cutaneous and mucosal surfaces [2]. The expression of desmosomal proteins such as desmoglein 1 and 3 (Dsg1 and Dsg3), desmocollins (Dsc) and plakoglobin in normal anagen hair follicles is similar to that of the adjacent interfollicular epidermis [3]. Therefore, pem-

Fig. 1. Overview of common types of alopecia in adults (adapted from Xu et al. [1]).

phigus can be characterised by erosions, alopecia and scarring due to the immune response mounted against hair follicles.

In deeper layers of the epidermis, the basement membrane zone (BMZ) consists of hemidesmosomes, specialised transmembrane complexes that mediate epithelial keratinocyte binding to the underlying basement membrane [2]. Hemidesmosomes express proteins including bullous pemphigoid 230 and 180 antigens (BP230 and BP180), and in hair these are concentrated in the upper and middle portions of the follicle and gradually lost in the lower part of the follicle [4]. Autoantibodies against BMZ components in pemphigoid disorders seem to be

responsible for the incomplete ultrastructure of hemidesmosomes to lead to blistering and hair loss [5].

The differential diagnosis of these patients' hair loss can include the primary disease process as well as secondary causes of cicatricial or non-cicatricial alopecia (Fig. 1). This diagnosis is based on the patient's history, various hair evaluation methods and scalp histopathology, including direct immunofluorescence [6–10].

Complaints of diffuse or localised alopecia have generally been overlooked in patients with severe blistering disease because it is regarded as a cosmetic issue [11–13]. This review addresses the pathogenesis and clinical features of alopecia in rare AIBD, including the pemphigus

Table 1. Overview of cases with alopecia organised by blistering disease

Study	No.	Age, years/ sex	Patient origin	Skin involvement		Hair involvement		Alopecia pattern (cases)					
				type	severity	duration	pattern	alopecia at start	onset age, years	duration	patchy	diffuse	total scalp
Rosin [17], 1985	1	58/F	USA	PF	-	3 weeks	AA	Y	58	5 weeks	X	-	-
	2	35/M	Japan	PV	-	11 years	TF	N	25	10 years	-	-	-
	3	39/M	USA	PV	severe	12 years	TF	N	29	10 years	X	X	-
	4	70/F	-	PV	-	10 days	AE	Y	70	1 month 10 days	X	-	-
Jappe et al. [21], 2000	5	52/M	-	PV	-	6 years	AE	N	-	-	-	-	-
	6	37/F	-	PV	-	2 weeks	AE	Y	37	2 weeks	X	X	-
	7	27/M	-	PV	-	23 years	TF	N	11	16 years	X	-	-
	8	47/M	Korea	PV	-	1 week	AE	Y	47	1 month	X	-	-
	9	58/M	India	PV	-	6 months	AU	Y	31	27 years	-	-	X
Koslu et al. [24], 2009	10	av. 51/15 M, 8 F	India	21 PV, 2 PVeg	2 severe 16 moderate 5 mild	5 months	AE	-	-	-	-	-	-
Mlynek et al. [25], 2009	11	14/F	-	PF	severe	6 months	NSNS	Y	14	8 months	X	-	-
Fujii et al. [26], 2011	12	46/F	Japan	PV	-	4 months	NSNS	N	46	3 months	-	X	-
Ko et al. [27], 2011	13	51/M	Korea	PV	-	20 years	TF	Y	31	20 years	-	-	-
Hadayer et al. [28], 2013	14	32/F	-	PV	-	2 years	NSNS	N	-	-	X	-	-
Veraitch et al. [29], 2013	15	av. 50/ 1 M, 4 F	Japan	PV	2 mild, 3 moderate	-	AE	Y (3/5) N (2/5)	-	-	X (5)	-	-
Daneshpazhooh et al. [30], 2015	16	av. 46/50 M, 46 F	Iran	PV	16 moderate, 80 severe	-	AE	-	-	-	-	-	-
Fard et al. [31], 2017	17	av. 43/19 M, 33 F	Iran	PV	av. moderate	-	AE	-	-	-	-	-	-
Yoshida et al. [32], 2017	18	62/F	Japan	PF/PV	-	2 years	NSNS	N	62	2 years	X	-	-
Brunsting and Perry [33], 1957	19	60/M	-	BPCP	-	5 years	NSS	N	-	-	X	-	-
	20	55/M	-	BPCP	-	5 years	NSS	Y	-	-	X	-	-
Slepyan et al. [34], 1961	21	56/F	Finland	CP	-	12 years	NSS	-	58	8 years	X	-	-
	22	61/F	USA	CP	severe	5 years	NSS	Y	61	-	X	-	-
MacVivar and Graham [35], 1966	23	av. 54/ 9 M, 1 F	USA	BPCP	-	10 years	NSS	-	-	-	-	-	-
Bairstow [36], 1971	24	66/F	USA	MMP	-	10 years	NSS	N	-	-	-	-	-
Stewart et al. [37], 1971	25	77/F	France	BP	-	8 years	PB	N	-	-	X	-	-
Lynfield et al. [38], 1983	26	57/M	USA	BP	-	1 year	AU	Y	21	36 years	-	-	X
Gibson et al. [39], 1986	27	35/M	USA	BPCP	-	1.5 years	NSS	N	35	8 months	X	-	-
Kurzahls et al. [40], 1995	28	78/F	Germany	BPCP	mild	7 years	NSS	N	82	-	-	X	-
Ball et al. [41], 1998	29	58/F	-	MMP	severe	4 years	NSS	N	-	-	-	-	X
Elston and Harman [42], 2006	30	50/M	Indonesia	BPCP	mild	2 years	AGA	Y	-	-	X	X	-
	31	39/F	Japan	MMP	-	8 months	NSS	N	39	-	X	-	-
De et al. [44], 2008	32	68/F	-	MMP	-	6 years	NSS	N	66	2 years	X	-	-
Martin et al. [45], 2009	33	63/F	-	BPCP	-	3 years	NSS	N	-	-	X	-	-

Table 1 (continued)

Study	No.	Age, years/ sex	Patient origin	Skin involvement		Hair involvement		Alopecia pattern (cases)				
				type	severity	duration	pattern	alopecia at start	onset age, years	duration	patchy	diffuse
Garcia-Garcia et al. [46], 2012	34	43/M	–	BPCP	–	6 months	AGA	Y	–	–	X	X
Pass and Dobson [47], 1965	35	62/F	USA	EBA	–	4 years	NSS	N	60	2 years		X
Palestine et al. [48], 1981	36	58/F	USA	EBA	–	11 years	NSS	N	–	–	X	X
Medenica-Mojilović et al. [49], 1987	37	61/F	–	EBA	–	4 years	NSS	N	–	–	–	–
	38	32/F	USA	EBA	moderate	6 months	NSS	Y	30	2 years	X	X
Rappersberger et al. [50], 1998	39	35/M	Africa	EBA	–	10 years	NSS	N	–	–	X	
Madan et al. [51], 2003	40	30/F	–	DH	moderate	2 months	AA	N	30	15 days	X	X
Yanagihara et al. [52], 2011	41	27/F	–	DH	moderate	2 months	AA	N	27	15 days	X	X
	42	35/M	Japan	LABD	severe	1 month	NSNS	Y	33	2 years		X

PV, pemphigus vulgaris; PF, pemphigus foliaceus; PVeg, pemphigus vegetans; av., average; BPCP, Brunsting-Perry cicatricial alopecia; CP, cicatricial alopecia; MMP, mucous membrane pemphigoid; BP, bullous pemphigoid; EBA, epidermolysis bullosa acquisita; DH, dermatitis herpetiformis; LABD, linear IgA bullous dermatosis; AA, alopecia areata; TF, tufted folliculitis; AE, anagen effluvium; AU, alopecia universalis; NSS, non-specific scarring; AGA, androgenic alopecia; NSNS, non-specific non-scarring; PB, pseudopelade de Brocq; Y, yes; N, no; -, information not available.

subtypes, BP, epidermolysis bullosa acquisita (EBA) and other subepithelial blistering diseases. The pathophysiology of individual blistering diseases is beyond the scope of this article; however, it may be reviewed separately in current diagnostic and therapeutic guidelines [14–16].

Materials and Methods

Search Strategies

We searched for relevant studies in Medline, PubMed and EM-BASE electronic databases up to September 2018. To maximise sensitivity, broad search terms such as “alopecia or hair loss or baldness” and “vesiculobullous disease” were used. Two authors (D.X. and A.B.-T.) independently examined titles, abstracts, then full texts of identified records for eligibility. Simultaneously, within relevant articles, published reviews and studies, the bibliographies that had cited these eligible records were also scanned. Neither language restrictions nor time period restrictions were imposed, and when uncertainty occurred, a third reviewer (D.F.M.) evaluated article eligibility.

Inclusion Criteria

We included non-randomised studies to provide evidence of outcomes that have not adequately been studied in randomised trials. With alopecia being an outcome that had not been highlighted as significant when previous randomised trials were conducted, epidemiological evaluation of the available literature can be very helpful in summarising the trends between small case series and cohorts. Additionally, alopecia is a relatively long-term and, in some types of blistering diseases, a rare complication, so preliminary evidence still demonstrates gaps and inconsistencies in the literature.

Empirical human studies that investigated the pathogenesis and clinical features of alopecia in the most common types of blistering skin diseases were to meet the following criteria: (1) population – patients of any age diagnosed with an autoimmune blistering disease; (2) intervention – evaluation methods for the diagnosis of blistering disease, including the type of alopecia; (3) comparison – any; and (4) outcomes – identification of participants with alopecia.

Outcome Measures

Our two primary outcomes were (i) the proportion of participants with alopecia from primary disease versus reversible causes and (ii) the type and severity of alopecia in AIBD.

Results

Description of Included Studies

Only 36 human studies of the 138 records retrieved from the databases fit our inclusion criteria, which included 223 patients (190 pemphigus, 25 pemphigoid, 5 EBA, 2 dermatitis herpetiformis (DH) and 1 linear immunoglobulin A, IgA, disease patients; Table 1). A sum-

Table 2. Summary of demographic and alopecia findings in autoimmune blistering diseases

	Pemphigus	Pemphigoid	EBA
Sex (F/M)	98/122	10/7	4/1
Age, years ¹	44.4±13.4	56.2±12.9	49.6±14.8
Duration of disease, years ¹	5.6±6.8	5.3±3.7	5.9±4.4
Duration of alopecia, years ¹	6.0±8.9	11.7±16.5	2±0
Alopecia at start, <i>n</i> (%)	9 (50.0)	5 (33.3)	1 (20.0)
Age at onset of alopecia ¹	39.1±19.3	51.7±0.9	45.0±21.2
Alopecia pattern, <i>n</i> (%)			
Patchy only	10 (71.4)	9 (64.%)	1 (33.3)
Diffuse only	1 (7.1)	1 (7.1)	0 (0.0)
Patchy and diffuse	2 (14.3)	2 (14.3)	2 (66.7)
Total scalp	1 (7.1)	2 (14.3)	0 (0.0)

EBA, epidermolysis bullosa acquisita. ¹ Mean ± SD; mean values exclude unavailable data.

mary of the epidemiological and alopecia variables is presented in Table 2.

A range of hair evaluation methods was demonstrated to reach alopecia diagnosis; only one study employed trichoscopy [29], seven studies performed the hair pull test alongside trichogram examination [20, 22, 24, 29, 30, 32, 53], and three studies performed either a hair pull test or trichogram [25, 31, 54]. For scalp pathology, 97 out of 232 cases were sent for vertical biopsies, potentially inclusive of some horizontal sections that were not made explicit in the methods. Despite this, horizontal sections were confirmed in 17 cases, and direct immunofluorescence was performed in 81 cases of alopecia.

In many studies, the overview of routinely collected data meant that we could not validate the diagnoses or assess the severity of blistering disease based on activity or damage scores. Only one study mentioned a validated disease scoring system in their methods [31]. Rather, we accepted severity scoring as mentioned by authors on the basis that a validated scoring system was used, otherwise information was classed as “not available.” Nevertheless, there is no universal scoring system for alopecia severity, so alopecia patterns have been analysed instead (Table 2).

Discussion

Pemphigus

There are two main types of pemphigus: PV and pemphigus foliaceus (PF) [55–57]. The pathological mechanism underlying alopecia in pemphigus has been studied in many animal species including mice, dogs, horses and

goats. Past knockout and active PV mouse model studies, together with the investigation of in vivo distribution of desmosomes, demonstrated the crucial role of Dsg1, 3 and Dsc in the anchorage of the telogen hair follicle [58–65]. Yet in humans, while scalp lesions are common in PV and PF, hair loss is often not a major finding. Therein lies a gap in the literature that this alopecic phenotype could be either specific for a genetic loss of Dsg3 or is peculiar to mice as opposed to humans. Recently, trichoscopy has also been regarded as a rapid and valuable tool in the differential diagnosis of AIBD, with the main findings in pemphigus presented in Figure 2 [6, 7].

Pemphigus Vulgaris

In PV, autoantibodies primarily bind Dsg3 and under certain circumstances Dsg1 expressed on keratinocytes, leading to loss of intercellular cohesion, and subsequently intraepidermal blisters and erosions of the oral mucosa particularly, and skin [66]. Anagen effluvium has been the characteristic hair loss in PV; however, “anagen shedding” has been suggested as more appropriate in that it does not also depict acute anagen arrest with loss of dystrophic hair shafts, such as from treatments of chemotherapy [3]. The Daneshpazhooh group [31] has made recent developments on the role of Dsg1 in human hair anchorage and hair loss, finding elevated anti-Dsg1 serum levels in PV-related anagen hair loss, yet interestingly no correlation between positive pull test and PV severity using total Pemphigus Disease Activity Index scores. The earlier investigation of Daneshpazhooh et al. [30] of 96 PV patients for hair loss had also found that 61% of patients had anagen shedding, associated with severe PV disease ($p < 0.01$).

Fig. 2. Trichoscopic features found in pemphigus including erythema and extravasations (**a**), dotted vessels (**b**), yellow haemorrhagic crusts (**c**), polygonal scaling (**d**), yellow diffuse scaling (**e**), white perifollicular scale (**f**), yellow perifollicular scale (**g**), white cotton wool-like areas (**h**) and brown peripilar sign (**i**).

Telogen effluvium is not commonly reported in PV patients, most likely because it goes unnoticed [67]. There remains no human evidence of a statistically significant correlation between PV and telogen effluvium, despite the literature containing separate research on physiological (and emotional) stress-induced PV, and stress-induced telogen effluvium alike [68–70]. Thus, the correlations between Dsg3 levels and telogen hair anchorage only remain studied in mouse models.

Inflammation Hypothesis. Normal anagen effluvium may even herald pemphigus, as it did in 1 patient (case 4) in whom hair shedding preceded skin lesions by 2 weeks [20]. There have also been 7 other cases linking PV inflammatory changes to anagen effluvium in Japan, South Korea and Israel [22, 28, 29]. Yet there remains the possibility that alopecia incidence is higher than reported because hair examination has not been routinely performed in PV patients without complaints of hair loss. Furthermore, tufted hair folliculitis and resultant scarring alopecia have also been seen in 4 separate cases in the literature, and these are proposed as being due to a host response to local scalp inflammation in PV [18, 19, 21, 27]. Saijyo and Tagami [18] were first to report a 35-year-old male with a recalcitrant PV scalp lesion where secondary bacterial infection led to tufted hair formation. This cycle of acantholysis and infection is what logically can cause local destruction to hair follicles and the resultant scarring alopecia (Fig. 3).

Antibody Hypothesis. In 2017, Yoshida et al. [32] reported a case of cutaneous PV without apparent mucosal lesions, which was associated with diffuse non-scarring alopecia. Despite a more dominant anti-Dsg1 to anti-Dsg3 antibody ratio normally seen in PF, suprabasal blisters were characteristically present in a likely case of cutaneous PV. Similarly, an earlier study observed a PV patient's initially high anti-Dsg3 to anti-Dsg1 ratio, in association with diffuse non-scarring alopecia as this ratio decreased [26]. Fujii et al. [26] suggest the involvement of anti-Dsg4 for the first time, with its detection in the epidermal suprabasal layers and hair matrix of their patient, despite its generally weaker expression than Dsg1 in hair follicles. Of note, the anti-Dsg4 defect is responsible for the sparse body hair seen in hypotrichosis, and its expression is known to depend on Smad-4, a transcription factor linked with progressive alopecia [71, 72]. Despite this idea, the detailed nature of anti-Dsg4 remains an enigma, and the cross-reactivity of antibodies should not be discounted in the pathomechanism of non-scarring hair loss in pemphigus.

Color version available online

Fig. 3. Lichen planus of the scalp in a 71-year-old female patient with bullous pemphigoid.

Pemphigus Foliaceus

The autoantibodies of PF are predominantly of the IgG type directed against Dsg1 [73]. Wu et al. [4] have sophisticatedly shown that in humans, Dsg1 is localised where more differentiated cells are, such as in the suprabasal epidermal layer, as opposed to the follicular bulge area which contains regenerative epithelial stem cells. In 1 case of juvenile PF associated with non-scarring alopecia, the observed prompt regrowth of hair after treatment may be attributable to the fact that this region is spared from autoimmune attack [25]. The aforementioned study by the Daneshpazhooh group [31] remains the only research into how Dsg1 antibodies have been linked to telogen hair anchorage and can contribute to the pathogenesis of alopecia.

Furthermore, a known association of pemphigus with other autoimmune diseases supports the occurrence of alopecia areata (Fig. 4) [17, 23, 52, 74, 75]. Specifically, a unique variant of multiple autoimmune syndrome described in a 58-year-old man with PV, alopecia universalis and insulin-dependent diabetes mellitus can be partly explained by the common link of these diseases to HLA class II haplotypes, i.e. HLA DR4 (case 9).

Pemphigus Vegetans

Pemphigus vegetans is estimated to make up 2–5% of pemphigus cases [76, 77]. These cases are characterised by

Fig. 4. A 51-year-old male with pemphigus vulgaris and a patch of alopecia areata on the scalp.

hypertrophic papillated plaques eroded from flaccid bullae (Neumann type) or pustules (Hallopeau type) commonly at intertriginous sites and oral mucous membranes. Yet scalp involvement in 4 cases, coexisting with typical lesions, has suggested that pemphigus vegetans also has a predilection for the scalp [78–80]. A clinical presentation including florid, verrucous and vegetative plaques appears to be associated with non-scarring alopecia [80, 81].

Basement Membrane Autoimmune Bullous Disorders **Bullous Pemphigoid**

There have been 16 cases of hair loss in the basement membrane group of chronic immunobullous disorders characterised by tense subepidermal bullae due to the deposition of antibodies against hemidesmosomal molecules in the BMZ [82–87]. Alopecia in BP has only been investigated in 2 individuals, including Lynfield et al. [38] who report on a Caucasian man with BP in the context of multiple autoimmune diseases, including alopecia universalis (case 26). The autoimmune aetiology of alopecia areata and its severer forms, alopecia totalis and alopecia universalis, has generally been supported, with many factors pointing to this pathogenesis, including its rapid response to steroid therapy, association with autoantibodies and other autoimmune diseases (refer to section “Pemphigus foliaceus”), as well as the presence of lymphocytic cells around hair follicles in active disease [38]. In light of this, a woman from France with BP and a curiously low rate of serum anti-BMZ antibodies has been described with the scarring pseudopelade of Brocq alopecia suggesting a perhaps lessened role autoantibodies may

play in the pathogenesis of this type of alopecia (case 25) (see aforementioned Fig. 3) [37]. Some common trichoscopic features are presented in Figure 5.

Mucous Membrane Pemphigoid (Cicatricial Pemphigoid)

Mucous membrane pemphigoid (MMP), or cicatricial pemphigoid (CP), is a chronic autoimmune bullous disorder that is characterised by autoantibodies against certain BMZ components to manifest predominantly on mucosal surfaces [15]. Perhaps it is due to the major sequela of MMP being scarring of the involved mucosa and skin, that severe scarring alopecia seems to be of a clinically insignificant severity in the majority of patients and is therefore rarely reported [44]. For example, it has been described as “persistent denudation of the scalp” in two cases, while a larger study reported scarring alopecia in only 4 of 54 patients [34, 41]. BMZ target antigens including BP180, BP230 and laminin 5 have been detected in hair follicles, so it is puzzling that gross scarring alopecia occurs only in a minority. As has been described in the hair growth cycle, immune privilege of the hair follicle may be the reason for follicle sparing in most patients with MMP. One dichotomous hypothesis is that either a minority of individuals must be susceptible to universal antibody binding to trigger a scarring alopecia, or there is a lack of BP230, BP180 and laminin binding in the scalp in most patients with MMP [41].

Brunsting-Perry CP (Localised CP)

In 1957, Brunsting and Perry [33] were the first to report 7 patients in whom unusual blistering confined to the head and neck resulted in scarring. Only 1 patient was described with non-specific scarring alopecia, of the 2 patients with scalp lesions. This type of BP has since been considered a localised form of CP, typically sparing the mucous membranes [88, 89], although extensive scarring alopecia and intense oral cavity erythema have also been noted in a woman with localised CP [45]. However, Brunsting-Perry CP seems to be consistently associated with non-specific non-scarring alopecia, as observed in 12 other cases [35, 39, 40]. Similar to Brunsting and Perry’s study, where 6 of 7 patients were balding men, a possible coexistence with androgenic alopecia has also been observed more recently in 2 cases of BPCP; however, the literature is not clear about how these presentations are related [42, 46]. As the onset of BPCP blisters in the former study started between the ages of 40 and 70, it is probable that non-specific scarring alopecia and androgenic alopecia in one individual are coincidental findings.

Fig. 5. Trichoscopic features found in pemphigoid, including extravasations (a), white diffuse scaling (b), linear serpentine vessels (c), yellow dots with whitish halo, “fried egg sign” (d), white cotton wool-like areas (e), white polygonal structures and thick arborizing vessels (f).

Epidermolysis Bullosa Acquisita

EBA's characteristic histopathology includes subepidermal blisters with linear deposits of IgG and C3 along the dermal BMZ [90]. Reports of scarring alopecia have been linked to antibody formation against collagen VII in the BMZ (Fig. 6) [91]. Yet even in severe cases, the scalp has been spared, despite extensive scarring, contractures and oesophageal dilatations, to suggest that the immune privilege of hair follicles is protective [92]. Nevertheless, alopecia has still developed during reduced expression of collagen VII in the corresponding genetic condition, recessive dystrophic epidermolysis bullosa, where immune privilege is arguably downregulated [3]. Pass and Dobson [47] described a case of EBA with diffuse alopecia, which was similarly defined in 2 out of 12 EBA patients between 1959 and 1979 [48]. Since then, two other cases linking non-specific scarring alopecia with the diagnosis of EBA

have been reported, with alopecia presenting as the first clinical sign of EBA in case 38 [49, 50].

Dermatitis Herpetiformis

DH is characterised by the deposition of granular IgA in lesional and perilesional skin, and its close association with coeliac disease [93]. Scalp lesions arise in 30% of cases, yet there have only been two studies reporting alopecia [94]. In a cohort study of 305 DH patients and 383 coeliac disease patients, the occurrence of associated diseases over an average period of 10 years was documented [95]. Of particular interest was the important but rare associations found with alopecia areata (1.6% DH and 0% CD). However, a limitation of this study was a lack of matched controls to contextualise these results. Nevertheless, the only two other cases described of DH and alopecia areata are in sisters [51].

Color version available online

Fig. 6. **a** Scarring alopecia and AIBD scalp lesions in a 49-year-old woman with epidermolysis bullosa acquisita (EBA). **b** Trichoscopic features found in EBA including loss of follicular openings, erythema and yellow haemorrhagic crusts.

Bullous Lupus Erythematosus

Approximately 5% of systemic lupus erythematosus is associated with subepidermal blistering caused by autoantibodies to the repeat region fibronectin III on collagen VII [92, 96]. While there are many reports of scarring alopecia in systemic lupus erythematosus, they do not seem to mention an association with the bullous phenotype [97–100]. Despite this finding, autoantibodies to type VII collagen characteristic of both EBA and bullous systemic lupus erythematosus have recently been shown to lead to blister formation by interfering with the NC1 domain, with which reports of scarring alopecia in EBA have been mentioned before [101].

Linear IgA Bullous Dermatitis

Linear IgA bullous dermatitis is characterised by small, tense subepidermal bullae caused by the linear deposition of IgA and sometimes IgG in the BMZ. Yanagi-

hara et al. [52] report a 35-year-old Japanese man presenting to hospital with full-body pruritic bullae, a sudden onset of visual disturbance, deafness, vitiligo and a 2-year history of hair loss. He was diagnosed with linear IgA bullous dermatitis associated with Vogt-Koyanagi-Harada disease, in the first reported co-existence of these two diseases. Whilst we cannot exclude the possibility of mere coincidence, the alopecia in this case could be part of a broader multiple autoimmune syndrome, especially in the presence of vitiligo, which is one of the most frequent dermatology disorders in multiple autoimmune disease [102].

Conclusion

It is clear that the literature regarding the pathogenesis of alopecia is incomplete, and the clinical features are inconsistent. This is arguably in part due to the rarity of the complication in some blistering diseases, as well as it being a complication that has not previously been deemed as worthy beyond a cosmetic stance to investigate. Yet more pertinently, there is a lack of a validated scoring system to assess the cause and severity of alopecia in blistering diseases, so therein lies a direction for our future research.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

This review is the original work of Danica Xie, who was involved in reviewing the literature, subsequent analysis of the data collected and writing of the final report.

Prof. Dédée F. Murrell, Dr. Asli Bilgic-Temel and Dr. Nada Abu Alrub were involved in the development of the initial study design and protocol as well as support in the editing of this paper.

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