

Antigen presenting cells in the skin of a patient with hair loss and systemic lupus erythematosus

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Abstract

Context: Hair loss is one of the most striking clinical features of active systemic lupus erythematosus (SLE), however, very few studies have investigated the immunological features of this process. **Case report:** We describe a 33 years old female who presented with scalp hair loss and arthralgias. Physical examination revealed erythematous plaques on the nose and scalp, with bitemporal hair loss. Scalp biopsies revealed epidermal hyperkeratosis, with a mild interface infiltrate of lymphocytes and histiocytes and a superficial and deep, perivascular and periadnexal infiltrate of mostly CD4 positive cells. Antibodies to HAM 56, CD68, CD1a, S-100, mast cell tryptase and c-kit/CD117 were strongly positive around the hair follicles, and in the adjacent sebaceous glands. **Conclusion:** We present the first report showing a significant presence of several antigen presenting cells around the hair follicular units in a patient with alopecia in active SLE. Today, antigen presenting cells and dendritic cells (DC) are modeled as the master regulators of human immunity. One aspect that has become clearly appreciated is the great diversity of DC subtypes, each with considerable functional differences. Thus, we suggest that APC and DCs are equipped with Pattern Recognition Receptors (PRRs) to some hair follicular unit antigens; that these innate sensors recognize conserved molecular patterns on self-tissue, and play a significant role in the pathophysiology of alopecia in SLE patients.

Keywords: Systemic lupus erythematosus, human, antigen-presenting cell, hair loss.

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Introduction

Many documented reasons exist for non physiological hair loss including medications, radiation, hormonal and nutritional factors, thyroid disease, generalized or local skin disease, and stress. Hair loss, or alopecia, is often met with significant emotional distress and anxiety. Healthy persons lose between 50-100 hairs a day; as part of the hair renewal process. Most people suffer from excessive hair loss at one time in their life [1]. After pregnancy many women experience a loss of hair, often caused by increased amounts of hair entering the resting (telogen) phase. Within two to three months after giving birth, some women will notice large amounts of hair coming out in

their brushes and combs [1]. This can last one to six months, but resolves completely in most cases.

Some prescription drugs may cause temporary hair shedding. Examples of such drugs include some of the medicines used for: gout, arthritis, depression, heart disease, high blood pressure, and anticoagulants [1]. High doses of vitamin A may also cause hair shedding. Chemotherapy and radiation treatment will cause hair loss because they both stop hair cells from dividing. Hairs become thin and break off as they exit the scalp [1]. The phenomenon typically occurs one to three weeks after the treatment. Patients can lose up to 90 percent of their scalp hair [1].

Hair loss may also be noted in people taking low protein diets. Hair loss may present in patients with diets insufficient in iron, especially manifested in women who have heavy menstrual periods or following major surgery. Women and men may have a genetic predisposition towards androgenic alopecia [1]. Since hormones both stimulate hair growth and cause hair loss, hormonal changes demonstrate a significant impact on hair loss [1]. Men generally have hair loss concentrated in a specific pattern from the front through to the crown. Women tend to have thinning throughout their head without being in any specific pattern [1]. This type of hair loss in both sexes is caused by the androgen dihydrotestosterone (DHT) [1]. Since everyone has DHT that is produced by their bodies and only selected people suffer from hair loss, another causative factor must be involved. The other factor is the possession of hair follicles that have a greater number of androgen receptors for the DHT to attach to; this is a critical component that is inherited [1].

Other causes of alopecia are immunological. Alopecia areata is one immunological cause of hair loss, and is believed to be caused by the immune system reacting to hair follicles and damaging them [1]. The hair loss is usually limited to a coin sized area and all the hair in the area is lost, leaving a very smooth, round patch. In a more severe, less common condition called "alopecia totalis", all hair on the entire body is lost, including the eyelashes [1]. Here we report a case a case of hair loss associated with active systemic lupus erythematosus (SLE). The case is of interest based on the fact that they are very few studies showing the immunological features associated with this process. In this case report we emphasize the importance of performing complete immunological testing when evaluating a patient with hair loss. The case is of importance based on the fact that the role of antigen presenting cells (APC) has, to our knowledge, never been reported in hair loss in patients with systemic lupus erythematosus (SLE). However, their presence has been reported in discoid lupus erythematosus (DLE).

Case Report

We describe a case of 33 years old female with a history of hypothyroidism (controlled with levothyroxine sodium, 112 mg) who complained of a rash on her face and chest for 6-8 wks with arthralgias. The patient had a past medical history of giving birth 6 months prior to presentation. The androgen dihydrotestosterone in her serum was normal. Her family did not have family members with androgenic alopecia; she had been diagnosed with parvovirus by a previous physician. She gave a history of SLE, apparently "controlled" with low dosages of oral prednisone. On examination, the patient presented a reticulated rash, as well as significant arthralgias. In the skin examination, the other notable findings were the presence of a few hypopigmented macules in her chest, small erythematous plaques on the nose, cheek, forehead, and upper chest, as well as an erythematous area on the left scalp and bitemporal hair loss. Given the constellation of findings, skin biopsies

were taken for hematoxylin and eosin (H & E) examination and direct immunofluorescence (DIF). The patient's laboratories at the moment of her skin exam displayed 710 units per μl of antinuclear antibodies (ANA), with a 1:640 homogeneous pattern. The SSA, (anti-Ro) test was positive, complement 4 (C4) levels were decreased, white blood cell count (WBC) also decreased ($3,4 \times 10^3/\mu\text{l}$) ($4.0-10 \times 10^3/\mu\text{l}$ normal values). Selected peripheral blood counts were decreased, i.e. basophils ($0.0 \times 10^3/\mu\text{l}$) ($0.1-0.3 \times 10^3/\mu\text{l}$ normal values), eosinophils ($0.1 \times 10^3/\mu\text{l}$) ($0, 1-0.6 \times 10^3/\mu\text{l}$), and neutrophils ($1, 8 \times 10^3/\mu\text{l}$) ($2, 9-6.2 \times 10^3/\mu\text{l}$). Thyroid testing values were all within normal limits. Other lab test including total peripheral blood protein, albumin, alkaline phosphatase, aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT), and total and direct bilirubin were within normal limits

Direct immunofluorescence (DIF)

In brief, four μm thickness skin cryosections were partially fixed in 3% paraformaldehyde, and incubated with the secondary antibodies (all fluorescein isothiocyanate (FITC)-conjugated). The following rabbit antibodies were utilized, directed to a), anti-human IgG (γ chain), b), anti-human IgA (α chains) c) anti-human IgM (μ -chain), d) anti-human fibrinogen, e) anti-human albumin from (all at either 1:20 to 1:40 dilutions), anti-complement 3c and C3D (C3c), (C3d) (all from Dako, Carpinteria, California, USA). In addition, we also used goat anti-human IgE antiserum conjugated with FITC (Vector Laboratories, Bridgeport New Jersey, USA), as well as goat-anti-human complement C1q (Southern Biotech, Birmingham AL, USA). Unconjugated rabbit anti-human IgE antibody was also used. The slides were counterstained with either 4',6-diamidino-2-phenylindole (DAPI), a fluorescent stain that binds strongly to DNA (Pierce, Rockford, Illinois, USA), or with Hoechst 33258 (Invitrogen, Carlsbad, California, USA), washed, and coverslipped. In addition, Pacific Blue goat anti-rabbit IgG (H & L) at 2mg/ml (Invitrogen) was also used as a secondary antibody for some of the unconjugated antibodies. Finally, anti-human-ICAM-1/CD 54 antibody (Lab vision Corporation, Fremont California, USA) was tested by using as its secondary Alexa Fluor[®] 555 goat anti-human antibody (Invitrogen).

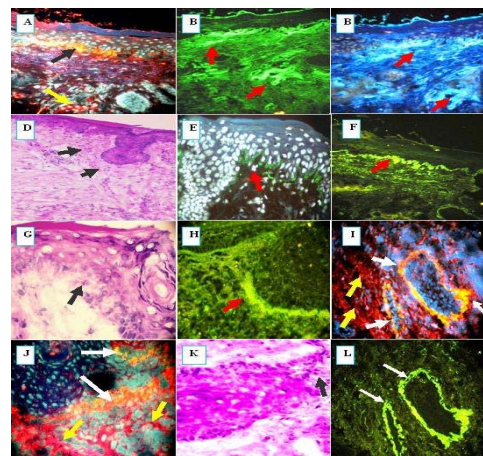


Fig 1 **a**, DIF (EX 395-410/490-505/560-585) shows positive deposits of anti-human C3 FITC- conjugated at the BMZ of the skin (black arrow), (yellowish staining). In the same figure, slightly under the BMZ, ICAM-1/CD54 was also overexpressed (orange-reddish staining) in the dermal vessels (yellow arrow). The nuclei were counterstained with Hoechst 33258, (grayish stain) (200x). **b**, shows strong deposits of anti-human fibrinogen antibody, conjugated with FITC in the superficial and deep vessels of the skin (yellow arrows), and in **c**, anti-human fibrinogen was also visualized, but in this case when using pacific blue as secondary antibody (++++) (blue stain) (yellow arrows), (200X). **d**. H & E demonstrates a mild epidermal hyperkeratosis with minimal follicular plugging. A mild, interface infiltrate of lymphocytes and histiocytes is noted, (black arrows) (100X). **e.**, DIF shows positive deposits of anti-human IgE-FITC conjugated (++++) (green staining) (yellow arrow) at the BMZ, with the nuclei were counterstained with Hoechst 33258, (grayish) (red arrow) (200x). Similar to **e**, but in this case, the nuclei were not counterstained 400X, (red arrow). **g**, H & E stain shows some atrophy of the epidermis, liquefaction of the BMZ and homogenization of the papillary dermis near the BMZ (black arrow) (200x). **h**. DIF shows strong deposits of anti-human IgG FITC-conjugated positive at the basal membrane area of the sebaceous gland (400X), (red arrow). **i**, DIF shows positive deposits of anti-human IgE FITC- conjugated (++++), around the BMZ of the sebaceous glands (yellowish staining) (white arrows). In the same figure, slightly under the BMZ, ICAM-1/CD54 was also very positive (orange-reddish staining) was overexpressed in some dermal vessels (yellow arrows). The nuclei were counterstained in this case with DAPI (blue stain) (200x). **j**, similar to the **i**, but at higher magnification for better detail (400x). **k**. H & E shows some mild spongiosis and BMZ degeneration of the hair follicle, with a mild cellular infiltrate of mainly lymphocytes and histiocytes (black arrow) (200x). **l**, DIF shows anti-human IgG-FITC conjugated (yellow staining) around the BMZ of the sebaceous gland (white arrows).

In Figure 1, a through j, are summarize the most notable patterns of H&E and DIF observed in this case including 1): the autoreactivity to the basement membrane zone (BMZ) of the skin (“lupus band”) and 2) autoreactivity to the sebaceous glands. We utilized a scale of 1 + (weakest staining) to 4 +++++ (strongest stain). The DIF displayed anti-human IgG (++++); IgM (++++); IgA (++, BMZ); IgE (++++); complement/C1q (+++); complement/C3 (++++); fibrinogen (++++); albumin (+) (all in a shaggy basement membrane zone (BMZ) pattern). An overexpression of anti ICAM-1/CD54 antibody (++++) was significantly observed at the vessels under the BMZ, as well as around some vessels in the reticular dermis of the skin.

Immunohistochemistry (IHC)

To study the correlation with numerous antigen presenting cells (APC) in the skin lesions and hair loss, we performed IHC utilizing a Dako dual endogenous peroxidase blockage system, with the addition of an Envision dual link following the manufacturers' instructions. We applied 3, 3 diaminobenzidine as a chromogen, and counterstained with hematoxylin. We tested for several antibodies including monoclonal mouse anti-human collagen IV (CIV) mast cell tryptase (MCT), CD4, HLA-DP, DQ, DR combined antigen antibodies, polyclonal rabbit anti-human CD117 (C-kit) and S-100. Finally, we also used mouse monoclonal anti-human antibodies to HAM56, CD1a, and CD68, (all myeloid/histiocyte antigen antibodies, and all from Dako).

Figure 2 shows the most important results, including the presence of a large population of antigen presenting cells (APCs), including those staining positive using the

myeloid/histoid HAM 56, CD1a, S-100 and CD68 antibodies. In addition, CD4, ICAM-1/CD54, anti-human IgE, C3, complement, MCT and c-kit also stained positive around the BMZ of the skin, and around the inflamed hair follicles and their associated, respective sebaceous glands.

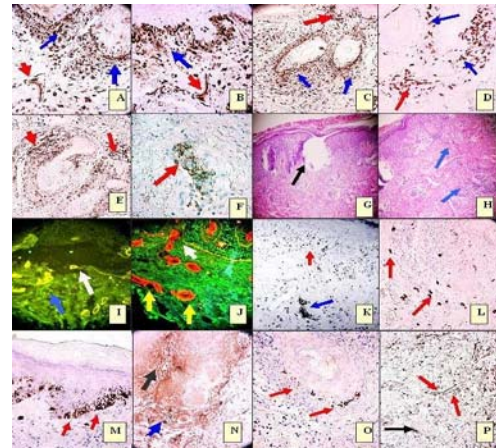


Fig. 2 **a** IHC, positive Ham 56 cells around the sebaceous glands (blue arrows) and around the adjacent vessels (red arrow). **b** Ham 56 antibody, positive under the BMZ in a linear distribution parallel to the BMZ (blue arrow), and also positive in the superficial vessels (red arrow). **c**. Positive CD68 cells, in a linear distribution under the BMZ (red arrow) and around the sebaceous glands (blue arrows). **d**. Positive myeloid/histoid cells around the hair follicles and the sebaceous glands (blue arrows), and also positive under a cluster of vessels (red arrow). **e**. CD4 positive cells around the sebaceous glands (red arrows) and in **f**, in clusters around the vessels (red arrow). **g**. H & E intraepidermal blister with strong liquefaction of the BMZ of the dermal epidermal junction (black arrow). **h**. In higher magnification, the atrophy and damage of the sebaceous gland and hair follicles is shown (blue arrows). **i**. and **j**, DIF showing the disrupted, dermal/epidermal junction of the skin (BMZ), using a monoclonal antibody to collagen IV (CIV) (yellow stain) (white arrows); please also notice some over-expression seen by the intense staining of the CIV antibody (++++) around the superficial vessels (blue arrows). In **i** we used CIV antibody FITC conjugated (yellow stain), and in **j** we used CIV antibody, but in this case we used as secondary antibody Texas red (red stain). **k**. Positive cells staining for HLA DR DQ DP in the superficial vessels (blue arrow) and under the BMZ (red arrow). **l**. Positive S-100 cells around the sebaceous glands (red arrows). **m**. C-kit/CD117 positivity at the dermal epidermal junction (BMZ) in a “band distribution.” (red arrows). **n**. MCT positivity around the dermal /epidermal junction of the skin (black arrow), and around the hair follicular unit (blue arrow) (brown stain). **o**. C-kit/CD117 positivity around the sebaceous glands (red arrows). **p**. MCT positive in the extracellular matrix as isolated cells (black arrow), and also some clustered around the vessels (red arrow).

Discussion

Hair loss can present one of the most important clinical features of active systemic lupus erythematosus (SLE). In our case, we followed a systematic approach to the study of hair loss, which enabled us to classify the hair problem in this patient. The correct diagnosis on the patient was based on a detailed history, physical examination, scalp biopsy and pertinent laboratory tests.

SLE is a chronic autoimmune connective tissue disease that can affect any part of the body [2]. As occurs in other autoimmune diseases, the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage [2]. SLE most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous

system [2]. The course of the disease is unpredictable, with periods of illness (called *flares*) alternating with remissions [2]. The disease occurs almost nine times more often in women than in men, especially between the ages of 15 and 50, and is more common in those of non-European descent [3, 4]. SLE is treatable through addressing its symptoms, mainly with corticosteroids and immunosuppressants; however, there is currently no cure for the disease [3, 4]. About 65% of people suffering SLE present with a dermatological issue at some point in their disease course. Most SLE immunologic studies have previously focused on testing the more common dermatological manifestations of SLE including the classic malar rash (or “butterfly rash”) [3-6]. Other studies had focused on studying the thick, red, scaly patches on the skin in discoid lupus patients [3-6]. Alopecia; and mouth, nasal, and vaginal ulcers are also common manifestations of SLE, but rarely studied from the immunological point of view [3-6]. In this report, we attempt to address this knowledge gap by focusing on testing some immunological markers and the antigen presenting cells that occur in alopecia in a patient with SLE. In our patient, we ruled out uncontrolled thyroid disease as a cause of alopecia (thyroid function was normal). We also discounted one of the most important causes for hair loss, a postpartum alopecia, due to the clinical timing of the hair loss

Some studies have found alterations of APCs in discoid lupus erythematosus (DLE), however, no immunologic studies have been reported in hair loss in SLE. The most common cutaneous subtypes of DLE are chronic DLE (CDLE) and subacute DLE (SDLE). CDLE is the only type of DLE which heals with scarring, and is commonly associated with hair loss. It has been hypothesized that the inflammation in CDLE generally involves the bulb area of the follicles (where the stem cells exist), with possible damage leading to permanent loss of follicles [4]. This finding has been reported based on the fact that cytokeratin 15 (an epidermal stem cell marker) is diminished and/or has been found absent in the hair bulb in the scarring lesions in patients with cicatricial DLE. [4]. In SLE, broader involvement of the hair follicles is noted in alopecia; the broader involvement has been attributed to the more widespread perifollicular inflammatory cell infiltrate in SLE. As far as we can tell by reviewing the literature, almost no reports have focused on studying the presence of antigen presenting cells (APC) and their relationship with hair loss in SLE.

In SLE, hair loss has been a controversial diagnostic criterion; indeed, it was not included in the American Association of Rheumatologists (ARA) criteria for diagnosis. However the ARA accepts that non-scarring, diffuse hair loss has been frequently observed in SLE patients. In regard to the pattern of hair loss and its frequency, one of the largest studies reported evaluated 122 SLE cases during the course of active SLE disease [5]. They found that 104 patients experienced at least one hair loss event before or during the course of SLE. In eighteen of those patients, patch alopecia was also found [5]. The

results suggest that non-scarring patch alopecia is an important pattern when testing patients for SLE [5]. Other authors had observed over the years that in lesions of DLE, the inflammation is usually more intense around the mid follicular level at the site where sebaceous glands are located [6]. The authors suggested that the sebaceous glands seem to be the first target in DLE, as is evident from significant, early histologic damage to the sebaceous glands (in the form of lymphocytic infiltration of the sebaceous glands, and the disruption of glandular structure) [6]. These findings are in agreement with ours. The authors suggest that it appears that the sebaceous glands are the first adnexal structures to disappear even before the hair follicles in DLE [6].

The first dendritic cells (DCs) to be discovered, in 1868 were the Langerhans cells of the human epidermis. It took however until the 1970s to demonstrate that these cells belong to the immune system. Simultaneously, in 1973, the pioneering work of Steinman and Cohn permitted the identification of DCs in lymphoid tissue and their functional relationship with Langerhans cells. Realization of the extraordinary capacity of DCs for antigen presentation set the stage for a, rising interest in their biology. Major advances in the early 1990s subsequently led to the ability to generate DCs *in vitro* from myeloid hematopoietic progenitors or from monocytes, and greatly facilitated their study. The initial unified model of DC life history held that immature DCs patrol peripheral tissues. Upon encounter with microbial and other unknown antigen products, the DCs undergo maturation as they migrate to lymphoid tissue, where they present antigen and activate naive T cells [7]. While most elements of this model still hold true, in particular the unique capacity of DCs to initiate adaptive immunity, many different and contrasting facets of DCs have since been discovered [8]. One aspect that has become clearly appreciated is the great diversity of DC subtypes, with considerable functional differences. Part of this heterogeneity is intrinsic (e.g. conventional versus plasmacytoid DCs), but a high degree of plasticity is also characteristic of the DC system. For instance, DCs can be instructed by the nature of the early signals they receive, with greatly divergent consequences on the immune response. Thus, in addition to their classic function to drive strong Th1-type adaptive responses, DCs can be polarized by microbial products towards a Th2-type response, or towards peripheral immune tolerance via the induction of regulatory T cells [9, 10]. Today, DCs are thus positioned as the master regulators of immunity. Pharmacological intervention to exploit the full range of DC regulatory potential will undoubtedly lead to a variety of therapeutic applications either to boost, suppress or repolarize the immune system [12, 13]. Another recently recognized important function of DCs is to link the innate and adaptive immune response. The link is illustrated by antiviral responses of plasmacytoid DCs [14], and by crosstalk between DCs and natural killer (NK) cells [15]. A major breakthrough in DC biology has been the recent unraveling of the mechanisms responsible for their regulatory functions, an advance made possible by the molecular cloning of genes expressed by DCs. Thus, it

was realized that DCs are remarkably equipped with Pattern Recognition Receptors (PRRs), the innate sensors that recognize conserved molecular patterns on microbes and self-tissue. Outstanding PRRs are the C-type Lectin receptors and the toll-like receptors. The key role played by chemokines and their receptors in the migration patterns of DCs is now well established. Finally, an array of cytokines and corresponding receptors are known to be responsible for the crosstalk between DCs and a host of other cell types that will determine the net outcome of the immune response. Collectively, this rapidly-evolving knowledge allows for drug-discovery programs to design pharmacological compounds to agonize or antagonize DC molecules in a number of clinical settings.

The two major APCs found in normal skin include the Langerhans cells (mostly located in the epidermis), and dermal dendritic cells. However, our study revealed a large and well defined pool of APCs with positive staining for HAM 56, CD68, S-100 and CD1a around the BMZ and the sebaceous glands of the attached hair follicles. We propose that these APCs may play a role either as an effector cells, or interacting with other cells (in our case, APC interaction with CD4 T cells and complement may mediate the immune process in the hair loss process).

Another unexpected finding was the presence of CD117/c-kit and MCT around the same sebaceous glands. Human mast cell tryptases (MCT) comprise a family of trypsin-like neutral serine proteases that are predominantly expressed in mast cells [16]. The mast cells play an active role in many diverse diseases. The CD117/c-kit antibody labels the transmembrane tyrosine kinase receptor CD117/c-kit, located in hematopoietic stem cells, melanocytes, mast cells, Cajal cells, germ cells, basal cells of the skin, and mammary ductal epithelia [16]. The proto-oncogene c-kit, localized to human chromosome 4, encodes a transmembrane receptor, CD117/c-kit, belonging to the class III receptor tyrosine kinase family, which includes the receptor for colony-stimulating factor 1, and the platelet-derived growth factor receptors type A and B [16]. Other authors have analyzed the relationship between the level of CD117/c-kit in peripheral blood mononuclear cells (PBMCs) and clinical activity in SLE [8]. The authors compared the c-kit expression in PBMCs in 47 patients with SLE and 21 healthy volunteers. They showed that the expression of c-kit messenger ribonucleic acid (mRNA) in PBMCs of SLE patients was increased, as determined by reverse transcription-polymerase chain reaction (RT-PCR). In addition, the c-kit receptor (CD117) was measured in their PBMCs by flow cytometry and was found to be increased in the patients with SLE [17]. Based on their results and on those of our study, we believe that the C-kit receptor, IgE, and mast cells, in addition to APCs, complement and immunoglobulins may all be of pathophysiologic importance in active skin lesions in SLE patients with alopecia. Further we detected some overexpression of CIV, which is a major constituent of the BMZ. HAM56 is another APC marker and also demonstrated positive staining around the BMZ,

and around the sebaceous glands. The HAM56 antibody labels human skin macrophages, tingible body and interdigitating macrophages within lymph nodes, and deep tissue macrophages. We also noted strongly positive CD4 staining in the cells around the BMZ and sebaceous glands. The CD4 protein is a transmembrane glycoprotein, and is expressed on normal thymocytes, T-helper cells, the majority of mature peripheral T cells, and a small subset of suppressor or cytotoxic T cells. The HLA-DP, DQ and DR staining were also weakly present in some cells around the superficial dermal vessels. The HLA antibody reacts with the alpha and beta-chains of all products of the DP, DQ and DR sub regions. These antigens belong to the histocompatibility (HLA) complex class II, or MHC class II. The antibody principally labels B cells, interdigitating reticulum cells, Langerhans cells and many non-Langerhans macrophages. It has been accepted that APCs play critical roles in establishing and maintaining peripheral tolerance. As described in most cases of lupus erythematosus, we observed the presence of strong autoreactivity to the BMZ (lupus-band) [18]. In addition, we were able to identify reactivity to the BMZ of the sebaceous glands, including staining with the anti-human IgE antibody. We also detected over expression of ICAM-1/CD54 in several vessels, both in the papillary as well as in the reticular dermis, as previously noted by others [19]. The presence of IgE has been previously described in patients affected by SLE directed to the kidney BMZ [19, 20]. The presence of these antibodies has been demonstrated to have a strong prognostic significance in the renal disease process, and light and electron microscopy showed more severe pathological changes in those with IgE positivity than in patients who were IgE negative [11,12]. However, the significance of IgE, MCT and C-kit at the BMZ of the skin and sebaceous glands in SLE is not presently characterized.

Of interest is that in mice models, the inflammation of modified eyelid sebaceous glands (the meibomian glands) has been specifically associated with active lupus [21]. In these mice models, the ocular disease is characterized by bilateral subacute and chronic inflammation of the eyelids (blepharitis) and hypertrophic meibomian glands. Therefore, we hypothesize that the presence of APCs, immunoglobulins and complement (especially located around the BMZ of the sebaceous glands) may play a pivotal role in this disease. Our statement is based on the fact that strong DIF staining with several antibodies, not only directed to the BMZ of the skin, but also at the BMZ of the sebaceous glands, was found in our case. Finally, our patient was treated with chloroquine orally 400 mg daily, combined with 40 mg of prednisone daily, and a mild steroid lotion in her hair and topical sunscreen. The patient's hair loss quickly improved. The full clinical and pathological significance of our findings are not known; thus, we recommend further investigation of the antigen presenting cells in alopecia in patients with lupus erythematosus.

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