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Lupus Erythematosus: Dermatologic Perspectives on the Diversity

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Abstract

Lupus is one of the complex autoimmune disease, which is difficult to diagnose and consists of few subtypes that are required to be classified. During our clinical work, we found out that the dermoscopy can be of great benefit to diagnose discoid lupus erythematosus (DLE). The histopathological examination is very important to confirm the diagnosis. The cases of infant LE patients, may derive the autoimmune antibodies from their mothers in order to diagnose the neonatal lupus erythematosus. Thus, it is very important to examine the antibodies of the mother, who may also be a subclinical LE patient and need continuous follow-ups or even treatment managements. Here, we present the cases of lupus with particular characteristics including linear cutaneous lupus erythematosus, DLE, and neonatal lupus erythematosus.

Keywords: lupus erythematosus, linear erythematous atrophic patch, neonatal lupus erythematosus, discoid lupus erythematosus, dermoscopy

1. Introduction

Systemic lupus erythematosus is a chronic, relapsing, inflammatory, and often febrile multisystemic disorder of the connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes. The word lupus means wolf in Latin, as the destructive injuries the disease caused brought to mind the bites of this animal [1, 2]. The earliest usage of the term lupus in the English literature is in the tenth century biography of St. Martin, written in 963 AD. However, the modern period of our understanding of this disease began in 1948, when Mayo Clinic hematologist Malcolm Hargraves [3] discovered the LE cell.

Lupus is all known as a spectrum disease, the symptoms between patients varies from mild to severe and can be divided into systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE). CLE includes three subsets of LE-specific skin diseases: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE). CCLE encompasses discoid lupus erythematosus (DLE), lupus erythematosus tumidus (LE tumidus), lupus profundus (also known as lupus panniculitis), chilblain lupus erythematosus (chilblain LE), and lichenoid cutaneous lupus erythematosus-lichen planus overlap syndrome

(LE-LP overlap syndrome). CLE can occur as a manifestation of SLE or independent of SLE. Patients with SLE may also develop a variety of LE-nonspecific skin diseases, cutaneous disorders that lack histologic features of LE, but occur with increased frequency in patients with SLE.

On diagnosing a systemic lupus erythematosus, we have several groups of diagnostic criteria. The major positive characteristics such as swollen joints, butterfly rash on the face, photo-sensitivity, or hair loss helps in the confirmation of the diagnosis. The laboratory examinations such as double-stranded DNA antibody (ds-DNA), anti-nuclear antibody (ANA) and other autoimmune antibodies are regarded as the highest level of consideration.

A systematic approach should be taken because of the diversity and complexity of clinical and laboratory manifestations [4–6]. Clinical manifestations may be due to one or any combination of the following: disease activity from active inflammation or thrombosis, acute drug toxicity, chronic damage due to the effects of the disease or its treatment (such as lung fibrosis or atherosclerosis), or comorbidity (e.g., infection). It is important to take a detailed history and to perform a clinical examination, including vital signs and urinalysis, to establish the likely differential diagnoses and then to organize the relevant investigations, depending on the circumstances. In addition, when assessing disease activity with a view to planning treatment, it is necessary to determine the circumstances that may have led to a lupus flare (such as exposure to sunlight, infection, hormonal changes, or previous disease-related therapeutic change) as this will guide further investigation, treatment change and disease monitoring required thereafter.

However, there are many subtypes of lupus, such as discoid lupus erythematosus and neonatal lupus erythematosus that does not follow the standard diagnostic criterion. Here, we present four instructive case studies of lupus. We hope this chapter will enlighten the perspective on lupus.

2. Brief overview of dermoscopy

Dermoscopy is a noninvasive method that allows the *in vivo* evaluation of colors and microstructures of the epidermis. It has been widely studied in differentiating benign and malignant skin lesions. With dermoscopy the diagnostician's sensitivity to diagnose melanoma is 90% compared to 74% when the technique is not used. It helps to avoid unnecessary surgery and give dermatologist more perspectives to plan the surgery. The diagnose and differential diagnosis of hair and nail diseases are also getting advanced benefits since application of dermoscopy. And now, dermoscopy is expanding its role as a tool for the evaluation of inflammatory skin conditions such as psoriasis, lichen planus and lupus.

3. Case presentations

3.1 Case 1. Linear cutaneous lupus erythematosus distributed along a reverse Blaschko lines

A 15-year-old female presented with itching linear erythema on the left forehead for 3 years. The erythema extended gradually to the scalp and the left upper eyelid, distributed in a linear pattern over time [7]. The patient was healthy except the lesion. Family history was negative. Physical examination showed that she was in good conditions. Dermatological examinations showed a longitudinal erythema on the left side of the hairline, forehead and left upper eyelid distributed in "S" shape

pattern. The surface of forehead lesion showed obvious atrophy, telangiectasis and adhesive scales (**Figure 1a**).

Laboratory examination of routine blood and urine test results, liver and renal function were all normal. Serum IgG, IgA, IgM, IgE, rheumatoid factor (RF), CIC, ANA, Anti-ds-DNA, Anti-RNP, Anti-SM, SSA, SSB, Anti-SCL-70 and Anti-Jo-1 antibody were within normal limits. Complement 3 (C₃) 0.749 g/L (normal value, 0.785–1.52 g/L), Complement 4 (C₄) 0.121 g/L (normal value, 0.145–0.36 g/L). Histological examination showed follicular keratotic plugging, vacuolar alteration of the basal cell layer, thickening of the basement membrane, perivascular infiltration of lymphocytes in the dermis (**Figure 1b** and **c**), which led to the diagnosis of linear cutaneous lupus erythematosus.

She was treated with compound glycyrrhizin tablets (two tablets three times a day, containing 150 mg glycyrrhizin, 210 mg monoammonium glycyrrhizinate, 150 mg aminoacetic acid, and 150 mg methionine), hydroxychloroquine tablets (200 mg once a day), and topical application of 0.1% tacrolimus ointment (twice a day). After half a year of follow-up, the skin lesion was improved with no tendency of systemic involvement.

3.2 Case 2. Dermoscopic presentation of DLE

A 38-year-old male with rapidly progressing papules demonstrating the features of acne on the left prefrontal region accompanied with tenderness for 2 months (**Figure 2a**). The patient had been diagnosed as epifolliculitis and treated with mupirocin cream for 1 month with no improvement. Physical examination revealed erythema, papules, callus shells, and plaques on his left prefrontal region. The results of blood routine and serum immunological examinations were normal. The specificity examinations including circulating immune complex, C₃ and C₄, antinuclear antibodies, double-stranded DNA antibody (ds-DNA), SSA/Ro antibody, and SSB/La antibody showed no any significant findings. However, dermoscopy of the lesions showed that the erythematous base was interrupted by a prominent keratinization around the hair follicles and follicular keratotic plugging (**Figure 2b**) [8]. It clued for differentiating atypical discoid lupus erythematosus from epifolliculitis with dermoscopy, and dermoscopy guided biopsy yielded a definitive histopathological diagnosis of the case. Histopathological evaluation of the lesions revealed dilated follicular openings filled with cornified material, follicular plugging, a necrosed part of the stratum basale, and inflammatory cell infiltration of the perifollicular and shallow dermal layers, which indicated discoid

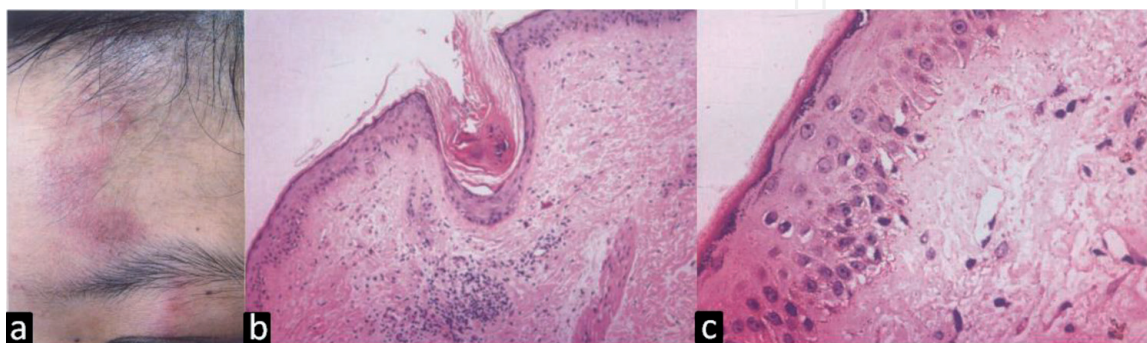


Figure 1. (a) A longitudinal erythema on the left side of the hairline, forehead and left upper eyelid distributed in an “S” pattern. The forehead lesion showed obvious atrophy, telangiectasis and adhesive scales. (b) Histological examination showed epidermal atrophy, follicular plugging, and the perivascular infiltration of lymphocytes in the dermis (HE stain $\times 100$). (c) Vacuolar alteration in the basal layer of the epidermis, and thickening of the basement membrane (HE stain $\times 400$).

lupus erythematosus (**Figure 2c**). The diagnosis of discoid lupus erythematosus (DLE) was confirmed. The patient received hydroxychloroquine 200 mg once a day, compound glycyrrhizin tablets (two tablets three times a day, containing 150 mg glycyrrhizin, 210 mg monoammonium glycyrrhizinate, 150 mg aminoacetic acid, and 150 mg methionine), and topical application of 0.1% tacrolimus cream once a day. The condition of the patient improved after 4 months of treatment (**Figure 2d and e**).

3.3 Case 3. Neonatal lupus erythematosus

A 3-month-old female infant presented with a butterfly-like edematous erythematosus on the center of her face, with raised border and scales (**Figure 3a**).

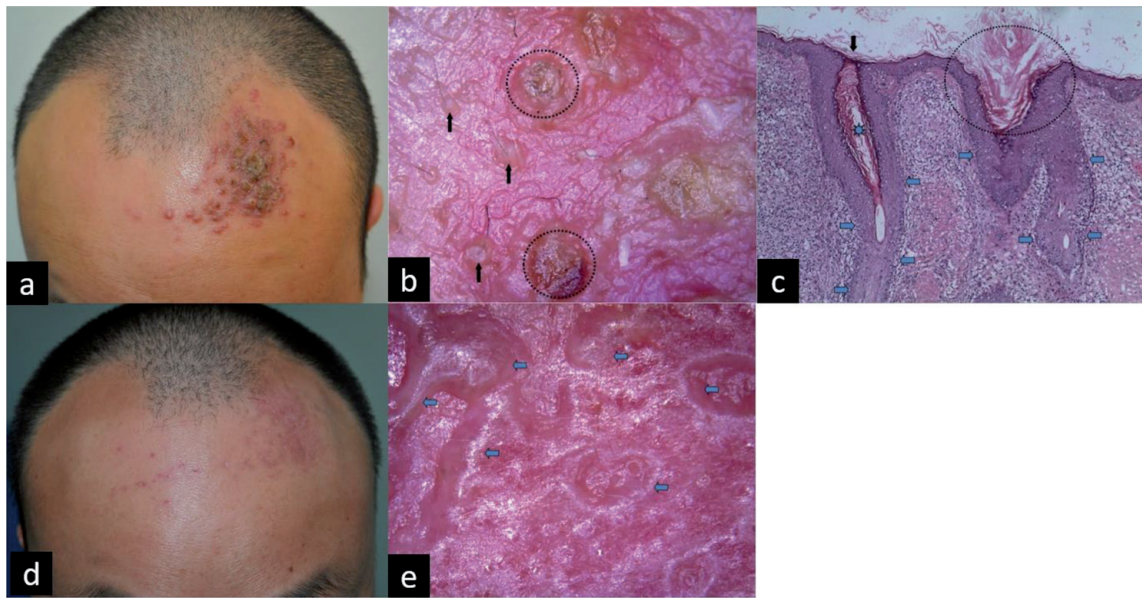


Figure 2.

(a) A 38-year-old male showed erythema, papules, callus shells, and plaques on the left prefrontal region. (b) Dermoscopic evaluation of the lesions showed an erythematous base interrupted by keratinization around the hair follicles and follicular keratotic plugging. (c) Histopathologic evaluation of the lesions revealed dilated follicular openings filled with cornified material, follicular plugging, a necrosed part of the stratum basale, and inflammatory cell infiltration of the perifollicular and shallow dermal layers, which indicated discoid lupus erythematosus (DLE) (HE stain, original magnification $\times 40$). (d) After more than 4 months of treatment, the condition improved obviously. (e) Dermoscopic evaluation of the lesions showed an erythematous scar instead of keratinization around the hair follicles, and follicular keratotic plugging.

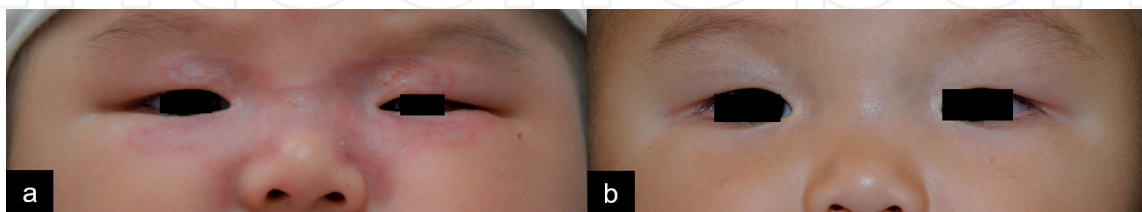


Figure 3.

(a) A 3-month-old female infant presented with butterfly-like edematous erythematosus on the center of her face, with raised border and scales. (b) After continuous treatment for 153 days with 0.03% tacrolimus cream once a day, and total glucosides of paeony capsules 300 mg once a day, the butterfly-like rash almost disappeared.

Due to the presence of scales on the lesion, a direct microscope examination with 16% potassium hydroxide (KOH), was done to rule out the fungal infection. However, the examination was not significant. In order to rule out congenital

syphilis, the *Treponema pallidum* particle agglutination assay (TPPA) and toluidine red unheated serum test (TRUST) tests were also done, with negative results. Finally, the autoimmune antibodies were examined. The report showed ANA (\pm), Anti-SSA (+++), and C_3 and C_4 were reduced. However, Anti-ds-DNA and rest of the anti-ENA examinations were not significant. The autoimmune antibodies of the patient's mother were not significant. The report showed ANA (+), Anti-SSA (+++) and Anti-Ro-52 (+++). Based on the manifestations, the final diagnosis of neonatal lupus erythematosus (NLE) was confirmed. The patient was treated with topical application of 0.03% tacrolimus cream once a day and total glucosides of paeony capsules 300 mg once a day.

After continuous treatment for 153 days, the butterfly-like rash almost disappeared (**Figure 3b**). After following up for 5 years, the conditions of both the patient and her mother improved with no features of lupus erythematosus.

3.4 Case 4. Neonatal lupus erythematosus baby and her SCLE mother

A 3-month-old female infant presented with butterfly-like rash on the center of her face since birth (**Figure 4a**). The dermoscopy of the lesion showed perifollicular whitish halo and telangiectasias (**Figure 4b**). It was quite similar with the most common dermoscopic criteria of LE.

Meanwhile while examining the mother's face, we found pink-red erythematous plaque on the center of her face (**Figure 4c**), which may get worse after sun exposure. And also, we found red edematous coin shaped patch on the left side of her face. Dermoscopy of the skin lesion showed typical telangiectasias manifestations (**Figure 4d**).

The autoimmune antibodies examinations of the infant showed ANA (1:100), Anti-SSA (+), C_3 and C_4 were reduced. And her mother's examination showed ANA (1:1000), Anti-SSA (+++), C_3 and C_4 were reduced. However, the ds-DNA and the rest of anti-ENA examinations were not significant.

The final diagnosis of the infant as neonatal lupus erythematosus (NLE), and her mother as SCLE were confirmed.

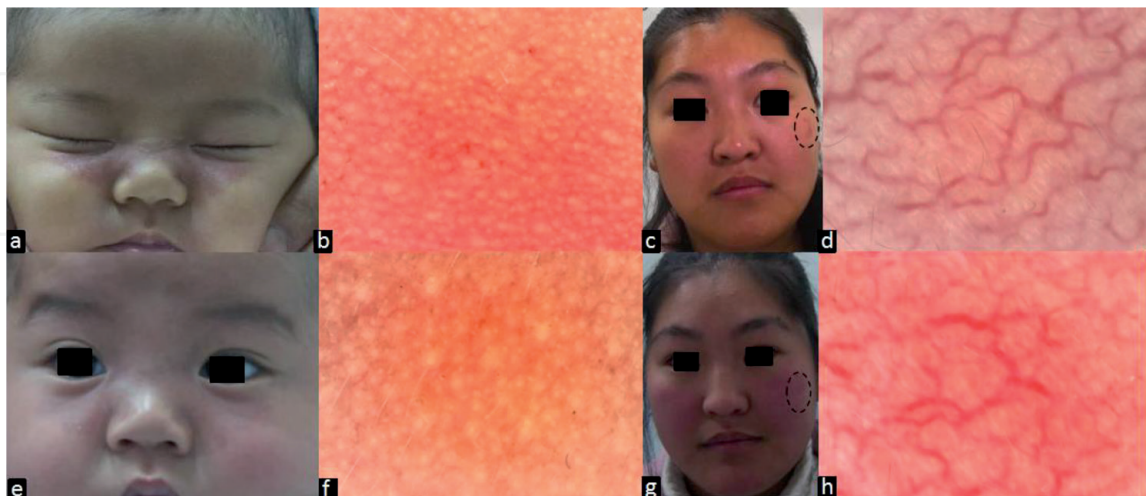


Figure 4.

(a) A 3-month-old female infant presented with butterfly-like rash on the center of her face since birth. (b) Dermoscopy showed perifollicular whitish halo and telangiectasias with a pink-red background. (c) The mother's face showed pink-red erythematous plaques on the center of her face, which may get worse after sun exposure. (d) Dermoscopy of the skin lesion showed typical telangiectasias manifestations with a pink-red background. (e) After 125 days follow up without medication, the baby's butterfly-like rash almost disappeared. (f) Dermoscopy showed the red background of lesion was lighter than initial performance. (g) After treatment for 125 days with 30 mg prednisone once a day, the skin lesion of the mother subsided. (h) Dermoscopy showed improved manifestations of telangiectasias.

The infant was given total paeony glycoside orally, but her parents did not implement it to her actually. The mother was treated with 30 mg prednisone once a day and was recommended to protect the skin from excessive sun exposure. The butterfly like rash of the baby almost disappeared when the follow-up after 125 days (**Figure 4e** and **f**), and the results of immunological examination were within the normal range. The skin lesion of the mother subsided (**Figure 4g** and **h**) and the re-examination of her autoimmune antibodies' examinations showed ANA (1:1000), Anti-SSA (+++) with no symptoms.

4. Discussion

Linear cutaneous lupus erythematosus (LCLE) is rare, and the skin lesions are mostly distributed along the Blaschko lines. The Blaschko lines, which was first described by and named by Blaschko in 1901, is the special lines on the surface of the human body. On the back of the trunk, the Blaschko line is V-shaped across the spine, and S-shaped on the anterior and lateral skins of the trunk. It exists in the form of vertical stripes on the skin of extremities, and is turbine-like on the surface of the abdominal skin and spiral-like on the scalp. The schematic diagram of the division of the facial Blaschko line was proposed see [9] in 1994, and it has different distribution patterns in different parts of the face. Discoid lupus erythematosus (DLE) lesion distribute along the Blaschko line in two Japanese children with the onset age being 3 and 11 years and the lesions located in the right cheek, left lower jaw and left neck, respectively in 1998 [10]. The authors analyzed the previous 6 cases and the current 2 cases, whereby they found that the 6 patients had an onset age of being smaller than 14 years, and that none of the patients had progressed into systemic lupus erythematosus. They argued that it might be a new subtype of lupus erythematosus, and proposed the name of linear cutaneous lupus erythematosus for DLE lesion with a linear configuration. In 1999 subsequently, an 8-year-old black boy with a lesion of LCLE along the Blaschko line in the right cheek and right chest, respectively see [11]; a 3-year-old Hispanic boy developed a lesion on his face and neck in 2002 see [12]. The lesion in our patient was located in the left forehead and left upper eyelid, which was formed S-shaped lesion, but was not distributed along the Blaschko line. This case was rather rarer and indicated that the skin lesion of LCLE was not necessarily distributed along the Blaschko line. In an adult case with linear, atrophic, plaque on left jaw and neck which did not follow the lines of Blaschko strictly [13]. But our case followed a reversed Blaschko lines (S shape line) on the left face.

As a matter of fact, the clinical presentations of DLE could be difficult to distinguish from other erythematous like patches and plaques. Thus, we highly recommend the use of non-invasive tool of dermoscopic technology to examine the details of skin lesions. The manifestations under dermoscopic findings of DLE could have erythematous base interrupted by prominent keratinization around the hair follicles and follicular keratotic plugging. According to the studies, follicular keratotic plug is one of the markers of discoid lupus erythematosus [14].

Another important method to confirm the diagnosis of DLE is histopathological examination. The typical features of DLE is follicular keratotic plugging, vacuolar alteration of the basal cell layer, thickening of the basement membrane, perivascular and periappendicular infiltration of the lymphocytes in the dermis.

Autoimmune antibodies such as Anti-Ds-DNA, ANA, ENA and immunoglobulins plays an important role in the diagnosis of SLE patients. However, in most conditions, the positive rate of antibodies could be very low in DLE patients. And in some patients no any manifestations are seen except the skin lesions.

SLE in children is fundamentally the same disease as in adults, with similar etiology, pathogenesis, clinical manifestations, and laboratory findings. However, it is generally accepted that children with SLE have greater disease severity and earlier accrual of disease damage than adults with SLE [15–19]. Worldwide, estimates of childhood-onset SLE incidence are between 0.3 and 2.2 per 100,000 children-years, while prevalence rates range widely from 3.3 to 9.7 per 100,000 children and adolescents, depending upon the population studied and its ethnic distribution [20–31].

Neonatal lupus is a rare syndrome that is associated with maternal antibodies to Ro/SSA, to La/SSB, and, much less frequently, to U1RNP. Infants develop eruptions characterized by erythematous arcuate patches or plaques with raised active margins shortly after birth. Congenital heart block is the most concerning complication of neonatal lupus. Following the birth of an infant with neonatal lupus, the risk for congenital heart block is increased with subsequent pregnancies [32]. Of note, treatment with hydroxychloroquine may decrease the risk of neonatal lupus (congenital heart block) in at-risk pregnancies [33].

The infant LE patients may derive the autoimmune antibodies from their mother in order to diagnose the neonatal lupus erythematosus. Thus, it is very important to examine the antibodies of the mother, who may also be a subclinical LE patient and need continuous follow-ups or managements.

For treatment, topical application of tacrolimus ointment is the most recommended therapy. Except one SCLE patient who had significantly increase titers of ANA and Anti-SSA, we used mild moderate dose of prednisone, all other LCLE, DLE and NLE did not give systemic prednisone, instead with compound glycyrrhizin tablets, or, total glucosides of paeony capsules which made from the extracts of traditional Chinese medicine. During our clinical practices, these medicines showed reliable efficiency and very few of side effect, with a favorable prognosis. In case 4, the skin lesion of neonatal lupus erythematosus baby spontaneously alleviated, suggested that it can remission without disposal, accompanied the autoantibodies from her mother decreases. But long-term follow-up is still needed.

5. Conclusion

In order to confirm the special clinical cases of lupus, such as linear cutaneous lupus erythematosus, DLE, or neonatal lupus erythematosus, the characteristics of dermoscopy and autoimmune antibodies tests are important. In these cases, topical tacrolimus, oral compound glycyrrhizin or total paeony glycoside, or, hydroxychloroquine had good prognosis, without systemic glucocorticoid therapy.

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