Chapter 1
Approach to Patients with Skin Manifestations

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In this presentation, I will discuss a hypothetical case of subacute cutaneous lupus erythematosus (SCLE) representing a mosaic of several real-life patients for whom I have personally cared over the past three decades. The case will be discussed at three different time points in the patient's disease course to illustrate my approach to the initial evaluation and diagnosis of such patients, recognition and management of adverse effects of treatment, and management of complications resulting from the failure to recognize clinical issues related to the development of overlapping autoimmune disorders over a patient's disease course.

My Initial Interaction with Patient

When I first see the patient, I want to know what part of the body on which the skin change or rash first appeared. Some skin conditions reveal their identities by the regional skin anatomy that they prefer or tend to avoid. For example, the early inflammatory manifestations of cutaneous dermatomyositis prefer the stretch areas over the knuckles of the hands and fingers, while early cutaneous LE inflammation prefers the hair-bearing areas of skin overlying the dorsal aspects of the fingers between the knuckles. I want to know whether the skin change has been present continuously throughout the present illness or whether it waxes and wanes and whether environmental stimuli are associated with such cycles.

I then question the patient about self-treatments with over-the-counter products that may have been used for the skin problem as well as prescription treatments that have been given by physicians prior to the patient's seeing me. Adverse reactions to

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prior treatments can sometimes mask the underlying primary skin problem. As an example, patients typically have used several over-the-counter products for their skin problem before seeing a dermatologist. When a topical sensitizing chemical (such as topical diphenhydramine, or Benadryl) touches the skin, a poison ivy-like allergic contact dermatitis reaction will develop several days after contact. Such superimposed, self-treatment-elicited skin changes can mask the underlying primary dermatologic process.

When managing chronic multisystem autoimmune disorders such as SLE, one must always keep in mind Greenwald's Law of Lupus. In 1992, Bob Greenwald, a rheumatologist, published his Law of Lupus. That law states that if a patient is diagnosed with SLE, there is a tendency to attribute (rightly or wrongly) everything that subsequently happens to the patient to SLE [1]. Banal skin changes such as rosacea are often confused with cutaneous LE by failure to apply this law. This is likely true for many of the connective tissue diseases.

Case Presentation

History of Present Illness. The patient is a 50-year-old white female who presented with a 6-month history of a persistent, non-pruritic rash that started initially on her arms and then spread to her upper chest, upper back, and neck. By history her central face had never been involved and she had never experienced similar skin changes below her waist. She had noticed that the rash worsened by sunlight exposure but indicated that some skin areas that were affected such as her shoulders and upper back were never exposed to sunlight. The patient had tried a nonprescription topical corticosteroid without benefit. Her primary care physician prescribed a topical cream containing both clotrimazole and betamethasone with only mild improvement of the rash. However, the rash returned quickly to its original appearance after this topical combination treatment was stopped.

Personal analysis of history of present illness. A chronic eruption presenting in an anatomical distribution such as this raises the question of a photosensitive cutaneous process (Table 1.1). The absence of pruritus argues against photosensitive disorders that are characterized by pruritus including cutaneous dermatomyositis, solar urticaria, a photosensitive drug eruption, and polymorphous light eruption. Cutaneous lupus is a photosensitive disorder that characteristically does not cause significant itching, but as always in medicine there are exceptions.

Some photosensitive disorders can display skin changes in areas not directly exposed to natural (sunlight) or artificial forms of ultraviolet light (e.g., cutaneous dermatomyositis, cutaneous LE, eczematous or lichenoid photosensitive drug eruptions) as well as in photoexposed areas. Typically, the rash starts in the areas of skin directly exposed to ultraviolet light and then spreads to contiguous nonexposed

Table 1.1 Photosensitive skin disorders[a]

Those not associated with a systemic illness
Photosensitive drug eruptions
Photoallergic contact dermatitis
Polymorphous light eruption and its variants
Solar urticaria
Those that can be associated with a systemic illness
Cutaneous LE
Cutaneous dermatomyositis
Porphyria/pseudoporphyria

[a]Extremely rare causes of photosensitivity not relevant to this discussion were not included in this table (e.g., Bloom's syndrome, xeroderma pigmentosum)

areas. Other photosensitive disorders characteristically produce skin involvement limited to areas directly exposed to ultraviolet light (e.g., polymorphous light eruption, solar urticaria, photoallergic contact dermatitis).

The patient denied using any over-the-counter topical products likely to contain contact-sensitizing chemicals (neomycin, bacitracin, diphenhydramine). Therefore, it is likely that the observed skin changes are the expression of the primary disease process rather than secondary changes produced by allergic contact dermatitis.

Clinical Context. The patient's Past Medical History includes mild hypertension over the past 5 years currently controlled with medical therapy. For the past 10 years, the patient had been under medical care for gastroesophageal reflux disease. The patient has a 20-year history of hypothyroidism. Review of Systems – The patient admitted to mild joint pains predominantly in her wrists and fingers over the past 3 months. She had also recently noticed the onset of malaise and easy fatigue upon exertion. Social History – The patient has smoked one-half pack of cigarettes daily for the past 30 years. Family History – The patient's mother had a history of alopecia areata and her younger sister developed vitiligo as a youth. Current Medications – Hydrochlorothiazide, lisinopril, omeprazole, and levothyroxine. Medication Allergies – None known.

Personal analysis of clinical context findings. Medical disorders such as hypertension and acid reflux disease are often treated with drugs that have the potential to cause photosensitive adverse skin reactions. Several of the medications that this patient is taking for her other medical problems fall into this category (e.g., hydrochlorothiazide, lisinopril, and omeprazole). In addition, these same drug classes have been reported to be capable of triggering drug-induced SCLE.

Early-onset hypothyroidism often results from autoimmune thyroid disease such as Hashimoto's thyroiditis. Individuals have had one end-organ autoimmune disease like autoimmune thyroiditis that is linked to the 8.1 ancestral HLA haplotype

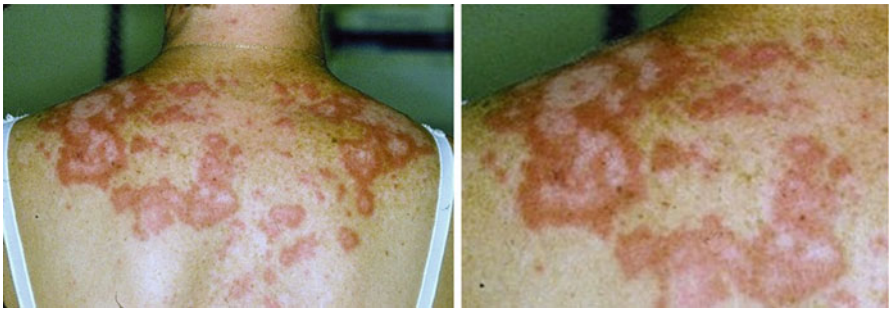

Fig. 1.1 Annular SCLE lesions. The *right panel* is an enlargement of the *left upper quadrant* of the clinical shown in the *left panel*. Note the light color of the skin within the inactive central parts of the annular lesions. Also note the polycyclic arrays resulting from the merging together of the larger annular lesions on the posterior aspects of the patient's shoulders

are at risk for developing other diseases that are linked to this haplotype (e.g., vitiligo, alopecia areata, SCLE, Sjögren's syndrome, type 1 diabetes mellitus, Addison's disease, pernicious anemia) [2].

The patient's recent onset of mild arthralgia, malaise, and easy fatigue would suggest the presence of a photosensitive skin disorder that is associated with systemic manifestations such as a cutaneous LE or cutaneous dermatomyositis rather than photosensitive skin disorders that are typically not accompanied by systemic inflammation (see Table 1.1).

If the patient proves to have a form of cutaneous LE, her history of cigarette smoking could result in a suboptimal clinical response to aminoquinoline antimalarial therapy [3].

Physical Examination. The patient was asked to disrobe and put on a hospital gown. The patient had papulosquamous skin lesions of varying size and shape distributed symmetrically on the lateral aspects of her neck, the V area of her upper chest, her shoulders, her upper back, the extensor surfaces of her distal arms, the extensor surface of her forearms, and the dorsal aspects of her hands. The smaller lesions were papulosquamous (i.e., red and scaly) papules and small plaques. However, the larger lesions were ring-shaped (i.e., annular) lesions with erythema and scale at the active edges and the absence of such changes centrally. The inactive centers of the lesions displayed a white-gray hue (i.e., leukoderma, meaning a decrease in or absence of melanin pigment) compared to the noninvolved perilesional skin (Fig. 1.1). In some areas, the annular lesions merged producing a polycyclic arrangement of lesions (Fig. 1.1).

There was no obvious dermal scarring associated with any of these skin changes. In addition, there was no periungual erythema on her fingers nor any

grossly visible periungual microvascular abnormalities. Bedside capillaroscopy with a dermatoscope failed to reveal any significant periungual microvascular abnormalities. In addition, there were no grossly visible cuticular abnormalities including hypertrophy or disarray. There was no tenderness, erythema, or swelling of the small joints of her hands and fingers. The ocular and oral mucosal membranes were not involved.

Personal analysis of physical examination findings. In a patient having a chronic rash of unknown etiology, it is important to have the patient disrobe and put on an examination gown so that a complete skin evaluation can be performed. Attention should be paid to pertinent negative findings as well as pertinent positive findings during the exam. For example, our patient indicated that her rash did not occur below her waist. However, subtle skin changes of disorders that can produce changes below the waist such as cutaneous dermatomyositis can be missed if the patient is not examined completely (e.g., patchy violaceous erythema over the lateral hips [holster sign], subtle violaceous erythema over the knees and medial malleoli). Most forms of cutaneous LE do not produce changes below the waist.

In addition, inflammatory skin changes on one part of the body can at times be secondary to a focus of skin inflammation on another part of the body. As an example, patients with inflammatory skin changes on their feet resulting from dermatophyte fungal infection can develop aseptic eczematous skin changes over their upper extremities and back as a result of the dermatophytid reaction (a fungus-triggered autoeczematization reaction) [4]. One can misinterpret the cause of the rash on the arms and back in this setting if one does not examine the feet to recognize the appropriate etiologic association.

There are four dimensions to the skin examination: (1) primary lesions, (2) secondary lesions, (3) lesional arrangement, and (4) regional anatomic distribution of lesions. The starting point in diagnosing a skin rash is to identify the primary skin lesions and any secondary skin changes that might be present, recognize any patterns resulting from how primary skin lesions associate with each other, and deduce the predominant regional anatomy targeted by the primary skin lesions. Questioning the patient about what the skin lesions looked like when they first appeared can help separate the earlier primary lesions from the later appearing secondary skin changes. Some might argue that awareness of pertinent negative physical exam findings might represent a fifth dimension of the physical exam. With respect to differential diagnosis, what a skin disease does not say about itself can at times be as important as what it does say.

The patient in question here had a papulosquamous eruption presenting in an anatomic distribution suggesting that sunlight exposure may have been a precipitating or aggravating environmental trigger. A key physical finding that distinguishes the skin lesions in this patient from those of other papulosquamous disorders was the tendency of the early small papulosquamous plaques to enlarge radially and regress centrally to produce annular lesions with leukodermatous centers unaccompanied by dermal scarring. This constellation of skin changes in the appropriate regional anatomical distribution is virtually pathognomonic of SCLE. (Other cutaneous annular inflammatory disorders such tinea corporis and erythema annulare centrifugum do not display leukoderma at their inactive centers).

The type of primary lesions, their pattern of physical association with each other, and their proclivity for affecting certain anatomic regions allow an experienced clinician to recognize a diagnostic pattern or clinical gestalt. However, the missing pieces of this gestalt necessary for a specific diagnosis must be filled in with diagnostic analysis (e.g., skin biopsy, laboratory results).

Workup to Confirm a Clinical Diagnosis of SCLE

A 4 mm punch biopsy of lesional forearm skin was performed on the active red scaly border of one of the annular lesions. The reported dermatopathologic findings of biopsy sections stained with hematoxlyn and eosin included a cell-poor interface dermatitis with increased dermal mucin infiltration (the increase in dermal mucin deposition was confirmed by special stains). These findings would be consistent with both cutaneous LE and cutaneous dermatomyositis and exclude the other photosensitive skin disorders listed in Table 1.1.

In addition, a separate 4 mm lesional punch biopsy was obtained from forearm skin for direct immunofluorescent examination. Reported results included a continuous band of IgG and IgM at the dermal-epidermal junction deposited in a discrete dust-like pattern. This finding would be much more typical of SCLE than cutaneous DM.

Venous blood was sampled for a complete blood count and a serum chemistry screen. Both assays were reported to be within normal limits. Antinuclear antibodies (ANA) and individual autoantibody specificities that are associated with cutaneous and systemic LE (SLE) (Ro/SS-A, La/SS-B, URNP, Sm) were assayed. The ANA was elevated at a titer of 1:320 and Ro/SS-A autoantibodies were present. The presence of Ro/SS-A autoantibodies would be more typical of SCLE than cutaneous dermatomyositis. In addition, an erythrocyte sedimentation rate and a urinalysis were reported to be within normal limits arguing against SLE disease activity. Also, the normal complete blood count and serum chemistry screen results argue further against SLE disease activity by excluding leukopenia, thrombocytopenia, anemia, renal dysfunction, and hyperglobulinemia.

The above biopsy and lab results would confirm a diagnosis of SCLE in our patient. The annular skin lesions displayed by this patient would allow subclassification as annular SCLE. Arthralgia, malaise, and easy fatigue are not uncommon in patients with untreated SCLE skin lesions. However, clinically significant inflammation in the vital internal target organs such as the kidneys and central nervous system are very uncommon in patients presenting with SCLE.

Management Strategies

Conventional approach. As the patient had previously failed strong topical corticosteroid therapy, it was felt that systemic therapy with hydroxychloroquine would be

indicated to treat both the patient's skin lesions as well as her mild musculoskeletal symptoms. The patient was started on hydroxychloroquine 200 mg by mouth twice daily following a baseline ophthalmological examination.

At follow-up in 8 weeks the patient had not substantially improved with respect to her skin inflammation. She was told that her cigarette smoking could be a factor in the failure of hydroxychloroquine to control her skin. The patient was encouraged to continue her efforts at discontinuing cigarette smoking including the possibility of starting oral varenicline (Chantix) through her primary care provider. She was then started on a compounded formulation of quinacrine at a dose of 100 mg/ day.

On follow-up 6 weeks later the patient had experienced marked reduction in her papulosquamous skin inflammation. Two months later the patient was free of skin lesions. At that time the hydroxychloroquine was decreased to 200 mg p.o. daily. The patient was told that it would be best for her to stay on antimalarial therapy for a total of 12 months before discontinuing this treatment in order to maximize the chance for an extended drug-free remission.

Alternative approach. Since the original description of SCLE, it has become increasingly clear that in addition to ultraviolet light, certain classes of medications prescribed for other medical problems can serve as environmental triggers for SCLE [5]. Discontinuing a triggering drug alone can result 6–8 weeks later in complete resolution SCLE skin disease activity without additional treatment. The representative SCLE patient described here had been on several classes of medications for other indications prior to onset of her annular SCLE lesions (a thiazide diuretic, an ACE inhibitor, and a proton pump inhibitor). However, there is no objective way to determine which of the drugs from these three classes if any might be triggering the patient's SCLE lesions. The only way to test this hypothesis is to work with the patient's other physicians to determine whether it would be possible to safely withdraw one or more of these three drugs from the patient's treatment regimen and avoid replacement with other drugs in the same class. Typically it would take to up to 2 months for the SCLE skin inflammation to respond clinically to the withdrawal of the triggering medication. However, in practice, this alternative management approach can be very difficult to coordinate and accomplish.

Interaction with the Patient One Year After My Initial Evaluation

The patient returned one year later complaining that her lupus skin disease activity was returning. About 3 months earlier she experienced a return of red scaly skin changes on her arms and upper back. These skin changes were more pruritic than they had been originally. There had been no interval change in her general medical status. She was still taking the hydroxychloroquine and quinacine. She denied starting taking any new medications over the last year.

Physical examination revealed the presence of skin lesions illustrated in Fig. 1.2. The new lesions were qualitatively different than those at the patient's initial

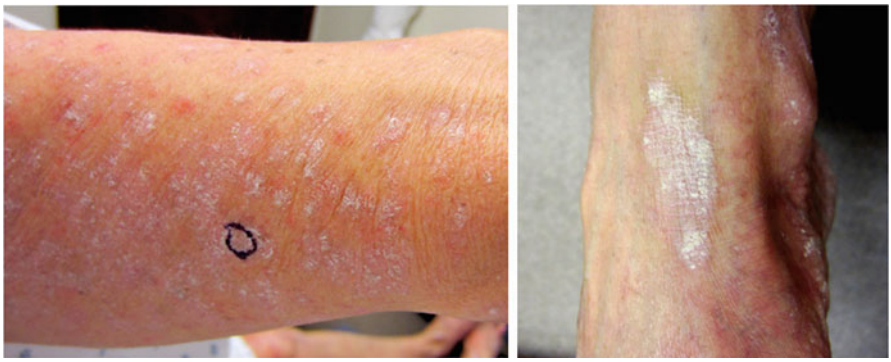

Fig. 1.2 Lichenoid drug eruption. *Left panel* – Note the small papulosquamous plaques on the extensor aspect of the patient's upper arm bearing confluent white scale (the *black circle* was drawn to indicate the location of a planned punch skin biopsy). *Right panel* – A papulosquamous plaque displaying thick adherent white surface scale on the anterior aspect of the patient's ankle

presentation 1 year earlier. In addition, the new lesions were present both above and below the waist. The new lesions were papulosquamous plaques of varied size with a thickened, adherent white scale. No annular lesions were evident.

Diagnostic possibilities for these new skin lesions included a return of SCLE disease activity with a shift from the annular to the papulosquamous clinical subtypes. However, the presence of the thickened adherent scale was not typical of any form of SCLE. In addition, SCLE lesions rarely occur below the waist. Perhaps the new lesions represented a shift from SCLE to classical discoid LE (approximately 20 % of SCLE patients will at some point in their disease course display typical discoid LE skin lesions). However, the new lesions lacked dilated, keratin plugged follicles and induration which are two hallmark clinical features of classic discoid LE skin lesions.

Another possibility for these new lesions would include precipitation of previously subclinical psoriasis, a recognized adverse reaction to antimalarial therapy. A skin biopsy could help address this possibility as the histopathology of psoriasis and LE-specific skin disease is quite different.

In addition, the patient could be suffering from a lichenoid drug reaction to one or a combination of the antimalarial drugs she is taking. The thickened hyperkeratotic nature of the new skin lesions and increased pruritus would be consistent with a hypertrophic lichen planus-like skin reaction.

A punch biopsy of the new lesions revealed a cell-rich interface dermatitis (syn. lichenoid tissue reaction). It was felt that the new skin lesions were most likely the result of a lichenoid drug reaction to the antimalarial drugs she was taking. The quinacrine was stopped but the hydroxychloroquine was continued. Over the following 2 months the new skin lesions melted away completely. On follow-up exam 3 months later, the patient's original annular SCLE skin lesions were still in remission.

Interaction with the Patient Two Years After My Initial Evaluation

At follow-up 24 months after her initial presentation, the patient was free of skin inflammation except for perlèche changes at the angles of her mouth. Over the previous 12 months she had been successfully withdrawn from hydroxychloroquine without signs of cutaneous LE recurrence. However, the patient indicated that over the past several weeks, she has been noticing progressive weakness in the muscles of her arms and legs. Within the last several days, this had gotten so severe as to make it difficult for her to get out of bed. She was brought to the clinic by her daughter in a wheelchair to have this problem evaluated. When questioned, the patient admitted experiencing increasing problems recently with dry eyes and dry mouth.

Upon exam, no cutaneous inflammation was noted other than the changes of perlèche. Muscle examination revealed flaccid weakness of the shoulder and hip girdle musculature. In addition the patient had poor control of her cervical muscles.

How might this new clinical problem be explained? One possibility would be the patient is developing an overlap syndrome with polymyositis or early dermatomyositis. However, it is quite unusual for SCLE to overlap with any form of inflammatory myositis.

Another possibility would relate to the patient's new symptoms of dry eyes and dry mouth and her new skin finding of perlèche. Perhaps she had developed an overlap with Sjögren's syndrome. It is not uncommon for patients presenting with SCLE to later developed features or Sjögren's syndrome over their disease course as both of these conditions develop in the context of the same 8.1 ancestral HLA haplotype.

The patient's muscle weakness could be explained by hypokalemia resulting from tubulointerstitial nephropathy that occurred as a result of an extraglandular autoimmune manifestation of Sjögren's syndrome. To address this possibility, the patient's blood electrolytes were measured. Her serum potassium level was 2.0 mEq/L. Upon potassium replacement and alkali therapy, the patient's muscle weakness resolved rapidly. She was then referred to a nephrologist for more definitive management of the tubulointerstitial nephropathy.

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