Journal of Autoimmunity 48-49 (2014) 14–19

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

The classification and diagnosis of cutaneous lupus erythematosus

Annegret Kuhn [a,b,*], Aysche Landmann [b]

[a] Department of Dermatology, University of Muenster, Germany
[b] Division of Immunogenetics, Tumor Immunology Program, German Cancer Research Center, Heidelberg, Germany

ARTICLE INFO

Article history:
Received 7 October 2013
Accepted 13 November 2013

Keywords:
Skin
Cutaneous lupus erythematosus
Classification
Diagnosis

ABSTRACT

Lupus erythematosus (LE) is an inflammatory connective tissue disease of generalized autoimmunity characterized by pathogenic autoantibodies and immune complexes, attributed to loss of immune tolerance. Cutaneous involvement, which appears in the majority of patients with the disease, can present as LE-specific or LE-nonspecific manifestations. The LE-nonspecific manifestations include e.g. vascular skin changes and may be associated with systemic organ manifestations or other autoimmune diseases. In contrast, the LE-specific manifestations encompass the various subtypes of cutaneous lupus erythematosus (CLE), which are classified as separate entities without or with less severe systemic organ involvement. In the "Duesseldorf Classification", CLE is subdivided into four different categories: acute CLE (ACLE), subacute CLE (SCLE), chronic CLE (CCLE), and intermittent CLE (ICLE). Differentiation between these subtypes is based on clinical features and average duration of the cutaneous lesions, but can also consider histological changes of skin biopsy specimens and laboratory abnormalities. In addition, direct immunofluorescence and photoprovocation may be applied to confirm the diagnosis in specific cases. Further investigations should be considered dependent on the clinical symptoms of the CLE patient and the results of the laboratory tests. A revised scoring system, the Cutaneous Lupus Erythematosus Disease Area and Severity Index (RCLASI) has recently been validated to assess disease activity and damage in CLE. In this review, we focus on the classification of CLE and the diagnostic procedures to identify and confirm the different subtypes of the disease.

1. Epidemiology

The incidence of systemic lupus erythematosus (SLE) in the general population varies according to parameters of the studied population, such as age, sex, race, ethnicity, and national origin. In Europe, the incidence of SLE ranges from 3.3 to 4.8 cases per 100,000 persons per year, while in the United States, the incidence of SLE has been reported to range from 2.0 to 7.6 cases per 100,000 persons per year [1]. Cutaneous manifestations appear in 72%–85% of patients with SLE and represent the first sign of the disease in 23%–28% of patients. Most studies evaluated the incidence of SLE, and epidemiological data of the different subtypes of cutaneous lupus erythematosus (CLE) have rarely been investigated [2]. In 2007, a study from Stockholm County, Sweden, suggested that subacute cutaneous lupus erythematosus (SCLE) with anti-Ro/SSA antibodies presents with an incidence of 0.7 per 100,000 persons per year compared with an incidence of SLE in Sweden of 4.8 per 100,000 persons per year [3].

2. ACR criteria

The criteria established by the American College of Rheumatology (ACR) for the classification of SLE include 11 clinical and laboratory features providing some degree of uniformity to the patient populations of clinical studies [4]. The clinical presentation of skin involvement in SLE, however, presents with a much broader spectrum, although 4 of the 11 ACR criteria include mucocutaneous lesions (malar rash, discoid lesions, photosensitivity, and oral ulcers). In particular, photosensitivity is poorly defined in the ACR criteria as "a result of an unusual reaction to sunlight by patient's history or physician's observation" [4]. Moreover, photosensitivity is not specific for SLE and can also be observed in other conditions, such as polymorphous light eruption (PLE) [5]. In 2012, the Systemic Lupus Collaborating Clinics (SLICC) revised the ACR criteria to improve the clinical relevance and to incorporate new knowledge in SLE immunology [6]. The SLICC criteria comprise 17 clinical and immunological criteria; for example, the criteria of non-scarring alopecia or synovitis were included, whereas "photosensitivity" is

* Corresponding author. Department of Dermatology, University of Muenster, Von-Esmarch-Strasse 58, D-48149 Muenster, Germany. Tel.: +49 (0)251 8352210, +49 (0)622 1423773; fax: +49 (0)251 8358947, +49 (0)622 1423749.
E-mail address: kuhnan@uni-muenster.de (A. Kuhn).

0896-8411/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2014.01.021

no longer listed. However, the SLICC criteria still have to be evaluated in routine clinical practice and it is unknown how much impact these criteria have on the representativeness of SLE patients in clinical trials.

3. Classification of skin lesions in SLE

The clinical presentation of the cutaneous manifestations in SLE shows great variety and, thus, has led to the differentiation into LE-specific and LE-nonspecific manifestations by histological analysis of skin biopsy specimens [7]. The LE-nonspecific cutaneous manifestations are commonly associated with SLE, but may also be present in other diseases, including vascular skin changes such as periungual telangiectasia, livedo racemosa, thrombophlebitis, Raynaud's phenomenon, and acral occlusive vasculopathy. Leukocytoclastic vasculitis, which can occur as palpable purpura or urticarial vasculitis (especially hypocomplementemic urticarial vasculitis), papular mucinosis, calcinosis cutis, nonscarring alopecia, and erythema multiforme are also defined as LE-nonspecific manifestations [8].

The LE-specific cutaneous findings encompass the various subtypes of cutaneous lupus erythematosus (CLE) and were subdivided into three different categories as defined by constellations of clinical features and average duration of the cutaneous lesions, histological changes of skin biopsy specimens, and laboratory abnormalities: acute CLE (ACLE), SCLE, and chronic CLE (CCLE) [7]. Since this initial formulation of the Gilliam nomenclature and classification system more than two decades ago, several attempts have been made to improve this system and to provide new approaches to the problem of classification the different manifestations of CLE [9–11]. In recent years, a further subtype with characteristic clinical, histological, and photobiological features, named LE tumidus (LET), has been analyzed and defined as a separate entity of CLE [12–14]. The course and prognosis in these patients are generally more favorable than in those with other subtypes of CLE and therefore, a revised classification system, including LET as the intermittent subtype of CLE (ICLE), was suggested in 2004 (Table 1) [9].

In 2004, the European Society of Cutaneous Lupus Erythematosus (EUSCLE) was founded to further characterize the various subtypes of CLE and to achieve a general consensus concerning evidence-based clinical standards for disease assessment. A study group of EUSCLE defined a core set of variables for the evaluation of the characteristic features of the disease, resulting in the development of the 4-page EUSCLE Core Set Questionnaire, which includes various parameters that are considered the most relevant features of CLE [15,16]. In a recent study, data of 1002 CLE patients from 30 centers were collected using the EUSCLE Core Set Questionnaire, and a statistical analysis of clinical and laboratory features was performed [17]. The results of this prospective, multicenter study suggested that the EUSCLE Core Set Questionnaire facilitates the analysis of clinical and laboratory features in patients with CLE and will contribute to standardized assessment and monitoring of the disease in Europe. In a further analysis, therapeutic agents applied in this study population were evaluated, demonstrating that sunscreens are successful as preventive agents, and topical steroids show a high efficacy, whereas antimalarials are still used as first-line systemic treatment [18].

Table 1
Subtypes of cutaneous lupus erythematosus (CLE).[a]

Acute cutaneous lupus erythematosus (ACLE)
Localized form
Generalized form
Subacute cutaneous lupus erythematosus (SCLE)
Annular form
Papulosquamous form
Chronic cutaneous lupus erythematosus (CCLE)
Discoid lupus erythematosus (DLE)
Localized form
Disseminated form
Lupus erythematosus profundus (LEP; LE panniculitis)
Chilblain lupus erythematosus (CHLE)
Intermittent cutaneous lupus erythematosus (ICLE)
Lupus erythematosus tumidus (LET)

[a] Modified after [9].

4. Clinical manifestations

4.1. Acute cutaneous lupus erythematosus (ACLE)

ACLE presents most commonly as the classic "malar rash" or "butterfly rash", which may only affect the skin transiently preceding the onset of a multisystem disease by weeks or months (Fig. 1A). The skin lesions typically begin with symmetric, small, discrete erythematous macules and papules in the central portion of the face, occasionally associated with fine scales that gradually become confluent. Erosions ane ulcerations of the oral and/or nasal mucosa are frequently accompanied with ACLE and facial edema may be severe in some patients [19,20]. Generalized ACLE is less common and its onset usually coincides with exacerbation of systemic organ manifestation and prolonged disease activity. It is characterized by a widespread, symmetrically distributed, maculopapular erythematous, sometimes puritic rash simulating drug eruption with accentuation of the UV-exposed areas. Hands, including palms, and feet are often involved, whereas knuckles are typically spared. Skin lesions of generalized ACLE may mimic a drug eruption or on rare occasions can simulate toxic epidermal necrolysis (TEN-like ACLE) [21].

4.2. Subacute cutaneous lupus erythematosus (SCLE)

The skin lesions of SCLE appear mostly in a symmetric distribution on sun-exposed areas presenting initially as erythematous macules or papules that evolve into scaly, papulosquamous or annular/polycyclic plaques (Fig. 1B). Approximately 50% of the patients show annular/polycyclic lesions whereas the other half present with papulosquamous or psoriasiform lesions; few patients develop a mixed form with both forms [22]. Individual annular lesions may expand and merge with polycyclic confluence and central hypopigmentation. As a "clue" of the disease, SCLE can subside with characteristic vitiligo-like hypopigmentation but does not lead to scarring as in DLE [23]. Skin lesions of SCLE can be triggered by UV light and by a number of different drugs, e.g. terbinafine, thiazide diuretics, allylamine antifungals, ACE inhibitors, and calcium channel blockers [24,25]. Recently, Wiznia et al. published a case report of a patient developing SCLE-like eruptions after receiving the chemotherapeutic agent gemcitabine [26]. Up to 50% of the patients with SCLE fulfill 4 or more ACR criteria for the classification of SLE [4]; however, subsequent studies have revealed that only 10%–15% of the SCLE patients develop severe systemic organ manifestations with mild courses [22]. SCLE can be associated with a distinctive immunogenetic background including the 8.1 ancestral haplotype, the common Caucasoid haplotype that is carried by most people who type positive for HLA-B8, -DR3.

4.3. Chronic cutaneous lupus erythematosus (CCLE)

CCLE includes three different forms of disease: discoid LE (DLE), LE profundus/panniculitis (LEP), and chilblain LE (CHLE).