Where is lupus hidden?

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Summary

Systemic lupus erythematosus is a prototypic but heterogeneous autoimmune disease. The major clinical symptoms and signs are reviewed, as well as the main immunological abnormalities. Emphasis is put on the role of long-lived autoimmune plasma cells, not affected by current immunosuppressants and biologics, which are responsible for refractoriness and relapses.

Lupus is a term that originates from Latin and means wolf. From the medical point of view, several diseases are hidden behind this term, such as lupus pernio, which is a chronic skin lesion associated with sarcoidosis; lupus vulgaris, which is an ulcerative skin disease associated with tuberculosis and lupus erythematosus, which is an chronic autoimmune disease that exists in several forms ranging from pure cutaneous lupus via subacute cutaneous lupus erythematosus to systemic lupus erythematosus (SLE). This article mainly focuses on SLE, a non-infectious, remitting, chronic inflammatory autoimmune disease with involvement of numerous organs, such as skin, joints, serous membranes, kidneys, blood cells, myocardium, endocardium and peripheral and central nervous system.

The disease is not only clinically very heterogeneous but it is also characterized by many different autoantibodies, which are not only directed against nuclear antigens and different underlying immunological mechanisms so that it is legitimate to raise the question if several diseases are hidden under the term SLE.

The clinical heterogeneity substantially may delay the early diagnosis of SLE especially when patients do not present typical cutaneous lesions, such as butterfly rash and mainly inner organs are involved. This has been improved since the introduction of antinuclear antibody (ANA) screening, which became widely used in the routine laboratory practice around 1980. The lag time between the onset and the diagnosis of SLE was some 50 months before 1980 [1], 25 months between 1980 and 1989 [2], 15 months between 1990 and 1999 and 9 months after 2000 [3]. Missing characteristic serologic diagnoses were one of the reasons why SLE was markedly less rare diagnosed and thus hidden in the pre-LE cell and ANA era.

Skin and mucocutaneous lesions

The skin is one of the most frequently affected organ systems in lupus erythematosus. One can discriminate between LE-specific and non-specific skin lesions [4]. The appearance of LE-specific
Box 1

**Classification of LE-associated skin lesions [5]**

**LE-specific skin lesions**
- Acute cutaneous LE (ACLE)
  - Localized ACLE
  - Generalized ACLE
  - Toxic epidermal necrolysis-like ACLE
- Subacute cutaneous LE (SCLE)
  - Annular
  - Papulosquamous
  - Mixed patterns
  - Chronic cutaneous LE (CCLE, syn. DLE)
- “Classic” DLE (a) localized (b) generalized
  - Hypertrophic (verrucous) DLE
  - Lupus erythematosus panniculitis/profundus
  - Mucosal LE
  - LE tumidus
  - Chilblain LE
  - DLE–lichen planus overlap

**Non-specific skin lesions**
- Cutaneous vascular disease
  - Vasculitis
    - (a) Leukocytoclastic 1. Palpable purpura 2. Urticarial vasculitis
    - (b) Panarteritis nodosa-like
  - Vasculopathy
    - (a) Degos disease-like
    - (b) Atrophy blanche-like
    - (c) Periungual telangiectasia
    - (d) Livedo reticularis
    - (e) Thrombophlebitis
    - (f) Raynaud’s phenomenon
    - (g) Erythromelalgia (erythemalgia)
- Alopecia (non-scarring)
  - “Lupus hair”
  - Telogen effluvium
  - Alopecia areata
- Sclerodactyly
- Rheumatoid nodules
- Calcinosi cutis
- LE non-specific bullous lesions
  - Epidermolysis bullosa acquisita-like bullous LE
  - Dermatitis herpetiformis-like bullous LE
  - Pemphigus erythematosus Sener–Usher
  - Bullous pemphigoid
  - Porphyria cutanea tarda
- Urticaria
- Papulo-nodular mucinosis
- Anetoderma/cutis laxa/mid-dermal elastolysis
- Acanthosis nigricans (type B insulin resistance)
- Erythema multiforme (Rowell’s syndrome)
- Leg ulcers
- Lichen planus

cutaneous manifestations, such as acute cutaneous LE, subacute cutaneous LE and chronic cutaneous LE, which are all photosensitive normally does not cause problems in relating them to lupus. In contrast, LE non-specific lesions can also occur in other diseases (box 1) [5].

**Musculoskeletal manifestations**

Nearly all patients develop musculoskeletal symptoms during the course of the disease. Arthralgia or arthritis, which may affect any joint with a predominance of wrist, hand and knee are reported in more than 90% of the patients. Usually arthritis is described as non-erosive, non-deforming, moderately painful, migratory and symmetrical manifestation. The frequency of the Jaccoud arthropathy, which is a deforming but non-erosive involvement of joints is lower than 5%; the most frequent joint deformities are ulnar deviation, swan neck, “Z”-thumb and hallux valgus [6]. A severe, erosive and deforming arthritis mainly of wrists and hands, which is clinically not distinguishable from rheumatoid arthritis, occurs in up to 3–5% of patients. The term “rhupus” is commonly used for this subgroup of patients describing a coexistence of SLE and rheumatoid arthritis. Rhupus patients presented significantly higher CRP levels and ESR and lower frequency of lupus nephritis than SLE patients without rhupus [7]. Five out of 7 rhupus patients were anti-CCP antibody (ACPA) positive with levels comparable to rheumatoid arthritis patients while SLE patients not [8].

Avascular osteonecrosis is a common complication in SLE occurring in about 12% of patients. Most frequently affected joints are the hips and knees. Shoulders, ankles elbows, and wrists involved in a lower frequency. Two third of patients had two or more joints affected [9]. Risk factors are glucocorticoids [10] and antiphospholipid antibodies [11,12]. MRI showing bone marrow oedema is very sensitive and specific in diagnosing very early osteonecrosis [13].

Myalgia is a common symptom in SLE whereas real myositis is a rare manifestation.

**Neuropsychiatric SLE**

Neuropsychiatric systemic lupus erythematosus (NPSLE) is a very heterogeneous organ manifestation in which several pathogenetic mechanisms may lead to a wide spectrum of clinical signs whereas sometimes the symptoms are not easily distinguishable from mechanisms that are not related to lupus, such as infection, medication, cerebrovascular disease or antiphospholipid antibodies. NPSLE includes the neurologic syndromes of the central, peripheral, and autonomic nervous system and the psychiatric syndromes observed in patients with SLE in whom other causes have been excluded (box 2) [14]. Recently the EULAR has published recommendations for the management of NPSLE [15]. A prospective analysis of neuropsychiatric events in an international inception cohort
comprising 1206 SLE patients shows that neuropsychiatric events are of variable frequency, most commonly present early in the disease course and adversely impact patients’ quality of life over time. Of note, events that are not attributed to SLE are more common than those due to SLE, although the latter have a more favourable outcome [16]. Especially seizure disorders and severe cognitive dysfunction are the result of general SLE activity or damage.

Headache is a very common symptom in SLE but it is hard to find out a real connection between this symptom and SLE. Therefore, the data about the frequency of headache in SLE strongly vary between 55 and 75% in the literature [17,18]. A meta-analysis did not identify any evidences that the prevalence of headache is increased or that a unique type of headache exists in SLE [19]. In SLE patients with headache, aseptic or septic meningitis, sinus thrombosis (especially in patients with anti-phospholipid antibodies), posterior reversible encephalopathy syndrome (PRES), cerebral or subarachnoid haemorrhage should be excluded [15]. Clinical signs of the PRES are headache, seizures, loss of vision, focal weakness, and altered mental function. MRI predominantly shows transient, white matter hyperintensities on T2-weighted images. Diffusion-weighted images reveal an increased diffusion coefficient indicating vasogenic edema. This manifestation occurs mainly in young SLE patients who are in an early stage of the disease. Focal deficits are not uncommon. It can be the presenting manifestation of lupus but non-lupus causes, such as hypertension, eclampsia, renal failure and immunosuppression should be considered [20].

During the last decade, it became clear that the neuromyelitis optica spectrum disorders (NMD), including neuromyelitis optica (NMO, Devic’s syndrome), longitudinally extensive transverse myelitis, and recurrent optic neuritis can occur in coexistence with SLE [21]. A big progress was made with the discovery of an NMO-specific IgG autoantibody [22], which is directed to the aquaporin-4 water channel, a component of the dystroglycan protein complex located in astrocytic foot processes at the blood-brain barrier [23]. Thus, the AQP-4 auto-antibodies helped to distinguish these NMOD as autoantibody-mediated conditions from multiple sclerosis. In SLE, anti-AQP-4 antibodies are only detectable in patients with a coexistent NMOD, they are not found in SLE patients without NMOD [21,24,25]. It was shown in a SLE inception cohort of 1046 patients who were prospectively followed-up up to 10 years that the lupus anticoagulant is associated with a future risk for the development of intracranial thrombosis and anti-ribosomal P antibodies precede psychosis [26]. The other autoantibodies against cardiolipin, 2 glycoprotein I and NR2 (N-methyl-D-aspartate glutamate receptor) included in this study do not contribute to the prediction of a neuropsychiatric event.

### Fatigue

Fatigue is a very common and important feature in SLE. Fifty to 92% of patients are affected. It is the most highly rated symptom by SLE patients compared to other commonly reported complaints, such as pain, anxiety and depression [27]. Disease activity and damage are poor indicators of fatigue [28]. There is an urgent need to better clarify the mechanism, which are responsible for fatigue.

### Lupus nephritis (LN)

LN is still the critical organ manifestation determining the prognosis of SLE. The patients only notice symptoms until they have developed nephrotic syndrome or renal failure. Therefore, a periodic screening of renal parameters including urinalysis for nephritic sediment and proteinuria, serum creatinine and creatinine clearance is recommended. In case of signs for renal involvement, a renal biopsy is urgently indicated to histologically evaluate it according to the classification revisited in 2004 [29,30] since clinical and laboratory data cannot predict the histological changes [31,32]. It has been known for decades that anti-dsDNA antibodies and low complement levels are associated with LN. But, these parameters correlating with global disease activity are not specific for

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**Box 2**

**Neuropsychiatric manifestations in SLE** [14]

**Central nervous system**
- Aseptic meningitis
- Cerebrovascular disease
- Demyelinating syndrome
- Headache (including migraine and benign intracranial hypertension)
- Movement disorder (chorea)
- Myelopathy
- Seizure disorders
- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis

**Peripheral nervous system**
- Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
- Autonomic disorder
- Mononeuropathy, single/multiplex
- Myasthenia gravis
- Neuropathy, cranial
- Plexopathy
- Polyneuropathy

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nephritis. For this reason, biomarkers that are more specific for LN are needed. Anti-C1q antibodies seem to correlate with and precede the development of LN, especially the proliferative forms [33,34] while negativity of anti-C1q antibodies is an indicator of a lack of a renal involvement [35,36]. A recent study shows the superiority of anti-C1q antibodies over anti-dsDNA antibodies to track renal activity [37]. The combination of anti-C1q antibodies, C3 and C4 provided the best performance for predicting LN flares. The presence of negative or normal values of anti-dsDNA antibodies, anti-C1q antibodies, C3 and C4 indicates that an active LN is unlikely [38]. Promising urine biomarkers that correlate with LN activity in longitudinal studies are chemokines (monocyte chemoattractant protein-1, MCP-1) [39], neutrophil gelatinase-associated lipocalin (NGAL) [40], tumor necrosis factor-like inducer of apoptosis (TWEAK) [41], proteomics [42] and CD4+ T-cells [43].

**Neonatal lupus erythematous (NLE)**

In general, the NLE can be differentiated into a permanent manifestation, such as congenital heart block (CHB), and transient syndromes, such as cutaneous, hepatic and hematologic involvement [44]. CHB is the strongest manifestation in an offspring that frequently leads to pacemaker implantation before adulthood [45]. The risk of an anti-Ro/SSA antibody positive woman is about 2% to deliver an offspring with CHB [46,47]. This risk is increased ten-fold in women who have had a previous child with congenital heart block [48]. Of note, the majority of mothers who have anti-Ro/SSA and/or anti-La/SSB autoantibodies do not suffer from SLE or related autoimmune diseases [44]. The IgG autoantibodies directed against Ro/SSA and/or La/SSB are transferred by transplacental passage from the maternal into the fetal circulation, which is the precondition to cause the disorder. As the mothers are usually asymptomatic, very often the autoantibodies against Ro/SSA and La/SSB are first detected after the diagnosis of NLE [44]. In mothers with known positive anti-Ro/SSA and/or La/SSB antibodies, a weekly fetal echocardiography screening is recommended to monitor for an abnormal PR interval within the vulnerable period of CHB between week of gestation 16 and 26, which may allow an early intervention to prevent irreversible damage of the cardiac conduction system [48].

**Immunological disturbances**

SLE is an immunologically driven disease. The almost complete ablation of the adaptive immune system with antithymocyte globulin and high doses of cyclophosphamide followed by autologous hematopoietic stem cell transplantation (HSCT) results in long-term treatment-free remissions in about 50% of patients with SLE who were refractory to conventional immunosuppressive therapies [49–51]. Thus, the immunosuppression provides the basis for the profound resetting of a healthy self-tolerant adaptive immune system with thymic reactivation [50,52,53]. The question is why the other half of patients relapses. So far, clear scientific answers are not available but at least three options might explain that. One explanation is that we could not observe a complete depletion of the autoreactive immunological memory in every patient after immunosuppression (unpublished data), which might contribute to the reactivation of the disease [54]. The second explanation might be based on the impact of the genetic background. The strength of the genetic influence seems to differ from patient to patient [55]. Less than 1–2% of patients with a monogenic form, such as deficiency of complement components (C1q, C4) or TREX1 will spontaneously develop lupus [56] while the gross of patients are susceptible to lupus due to a combination of genes associated with SLE. These genes often affect immune functions, e.g. type-I interferon signaling, immune complex processing, B- and T-cell signaling, etc. Each allele contributes only minimally meaning that a cumulative effect of several genes is required to markedly increase the risk of SLE [57]. Therefore, patients who are more susceptible to SLE will easier relapse due to environmental triggers than patients who are less prone. The third possibility is that some of the patients with relapse after immunosuppression plus HSCT were exposed to a strong environmental trigger.

This already illustrates the complexity of the etiopathogenesis of SLE summarised in figure 1. In addition to the genetic background environmental, epigenetic, ethnic and hormonal factors as well as the gender contribute to disturbances of the innate and adaptive immune system whereas especially the role of the innate immune system has become clearer recently [57–59]. A characteristic of SLE is the type-I interferon signature [60–62]. Obviously, neutrophil extracellular traps (NETs), first described by the group of Arturo Zychlinsky, play an important role in inducing type-I interferon in SLE. NETs generated by activated neutrophils are composed of granule and nuclear constituents (DNA, histones) that disarm and kill bacteria extracellularly [63]. In SLE, the degradation of NETs can be impeded due to DNase inhibitors and anti-NETs antibodies [64], which promotes the type-I interferon release by plasmacytoid dendritic cells. The failure of dismantle NETs correlates with the renal involvement [64]. Very recently, a distinct subset of neutrophils, low-density granulocytes has been identified as a source of type-I interferon release in SLE [65].

Type-I interferon itself or its response proteins are useful biomarkers of disease activity. We have identified SIGLEC1 as one of the most prominent type-I interferon regulated genes in monocytes. The expression of SIGLEC1 on monocytes analysed by flow cytometry correlates well with the disease activity score SLEDAI, anti-dsDNA antibodies and inversely with complement levels [66]. SIGLEC1 expression on monocytes is more sensitive than the direct measurement of type-I interferon level [67].
Factors contributing to the pathogenesis of SLE

Extensive autoantibody production is the consequence of these disturbances in the immune system. More than 150 different autoantibodies directed against nuclear antigens and cytoplasmic antigens, cell membrane antigens including blood and endothelial cells, phospholipid-associated antigens, nervous system antigens, plasma proteins, matrix proteins, and miscellaneous antigens are described [68]. The pathogenic autoantibodies among them can directly or indirectly via immune complex deposition induce pathology [69]. Antibodies are generated and secreted from plasmablasts and mature plasma cells. The maintenance of antibody levels is secured by long-lived plasma cells [70–72]. The long-lived plasma cells secrete antibodies independently of antigen contact, T-cell help and memory B-cells [73]. Therefore, these cells are considered as memory plasma cells. Autoantibodies can be secreted by long-lived plasma cells as shown in a murine model of lupus [74]. The adoptive transfer of plasma cells from lupus mice to immunodeficient Rag1−/− mice results in the production of antibodies, including anti-dsDNA antibodies exclusively by long-lived memory plasma cells leading to immune complex nephritis [75]. The important point is that long-lived memory plasma cells are resistant to irradiation, conventional immunosuppression and therapies targeting B-cells including rituximab and belimumab [54,73,76]. Thus, long-lived memory plasma cells residing in survival niches in bone marrow and inflamed tissues explain the chronicity of autoimmunity and why some of the SLE patients are extremely refractory to standard of care therapies. Active SLE is characterized by B-cell hyperactivity that is reflected by high numbers of newly generated MHC class II expressing plasmablasts in the circulation that correlates with disease activity and anti-dsDNA antibodies [77,78]. In contrast to long-lived memory plasma cells, the newly generated plasmablasts respond to immunosuppression and B-cell targeting therapies.

In summary, both short-lived plasmablasts and long-lived memory plasma cells contribute to autoantibody production (Figure 2). This differentiation of the autoantibody secreting cells is of high relevance for the development of therapeutic strategies because of the refractoriness of memory plasma cells. So far, few therapeutic options are available to target long-lived plasma cells as part of the autoreactive immunological memory. This is the above mentioned immunosuppressive regimen in combination with HSCT and the depletion of plasma cells with the proteasome inhibitor bortezomib, which is approved for the treatment of multiple myeloma. Bortezomib prevents the development of nephritis and impressively prolongs the survival of lupus mice due to plasma cell depletion [79]. Based on these findings, active SLE patients refractory to
standard immunosuppression were successfully treated with bortezomib (Alexander et al., submitted). These proof of concept studies demonstrate that the auto-reactive plasma cell memory, which had been hidden for a long time is now one of the key therapeutic targets with a curative potential. It encourages identifying strategies for a selective targeting of pathogenic memory plasma cells.

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