Dear Editors,

Cutaneous lupus erythematosus (CLE) is an autoimmune skin disease which may occur isolated or in the context of systemic lupus erythematosus (SLE). A histological hallmark is interface dermatitis which is characterized by keratinocytic cell death induced by auto-aggressive T-cells. Common triggers include ultraviolet (UV) radiation, cigarette smoke and drugs. Both innate and adaptive immune system signaling pathways are involved in a repetitive inflammatory loop as reviewed earlier [1, 2].

Vitiligo is a frequent autoimmune pigmentation disorder characterized by T-cell driven destruction of melanocytes. Common internal and external triggers include genetic predisposition, viral infections, oxidative stress and drugs [3].

Herein we describe a case of a 59-year old female patient who developed scaly skin lesions one week after intense sun exposure. There was no comorbidity except Hashimoto’s disease. Anti-Sjögren’s syndrome related antigen A/B (SSA/SSB)-antibodies were detected with high titers, a lesional skin biopsy of the forearm confirmed subacute CLE (Figure 1). Systemic lupus erythematosus could be excluded in the absence of organ involvement. High-potency topical corticosteroids (TCS) and hydroxychloroquine treatment led to quick amelioration of inflammatory skin lesions, however, an asymptomatic depigmentation of previously affected areas evolved. In the following summer slight repigmentation could be observed from the edges without further specific topical therapy under continued systemic treatment with hydroxychloroquine (Figure 2). The patient rejected both a biopsy of the depigmented areas and a therapeutic approach with topical tacrolimus ointments as she felt no impairment by the discoloration. Affected skin has remained unchanged for another eight months until now; there were no further flares of CLE. We considered this phenomenon either as newly arisen vitiligo-like depigmentation due to the heavy flare of subacute CLE and hydroxychloroquine treatment or as true vitiligo in the course of CLE.

Association of lupus erythematosus and vitiligo has repeatedly been described in the literature [4]. Furthermore, there are sporadic reports about de novo vitiligo in CLE lesions and vice versa [5]. Cutaneous lupus erythematosus and vitiligo share distinct pathogenetic features as follows [6]: type I and type II interferon (IFN) and associated cytokine release leads to recruitment of cytotoxic T-cells via their corresponding CXCR3-receptors to specifically attack epidermal cells (keratinocytes and melanocytes) in both conditions. Major IFN-producers in this context are plasmacytoid dendritic cells (pDCs) and keratinocytes themselves [7]. Our group earlier described the striking similarities between the inflammatory reaction of autoimmune diseases associated with interface dermatitis [8] and the mechanism of regression in melanocytic lesions [9]. A specific trigger for

![Figure 1](image1.png) Dermosthistopathology of a lesional skin biopsy of the right arm in June 2018 displaying an orthokeratotic thin epithelium infiltrated by numerous lymphocytes resulting in degeneration of the basal membrane as well as formation of colloid bodies and pigmentary incontinence, consistent with diagnosis of subacute cutaneous lupus erythematosus (hematoxylin-eosin stain).
the release of IFN is the detection of extracellular DNA as a result of various triggers like UV radiation. Keratinocytes expressing heat shock protein 70 (HSP70) in course of danger signals may potentiate this effect [10]. Apart from that, CLE is defined by high photosensitivity as UV exposure causes a variety of pro-inflammatory effects (e.g. release of reactive oxygen species and release of mast-cell factors) that ultimately result in cellular damage [1]. The Janus-kinase (JAK)-signal transducer and activator of transcription (STAT) pathway as IFN-associated downstream effector pathway is a promising therapeutic target for both CLE and vitiligo [11]. A summary of specific and common features of CLE and vitiligo is provided in Table 1 [1, 3, 11, 12]. It is noteworthy that isomorphic response is a feature not limited to vitiligo but also present in subtypes of CLE [13]. Numerous drugs bear the potential to trigger CLE and vitiligo; some drugs and biologics like immune-checkpoint-inhibitors may even elicit both [14, 15].

In this case, we could not obtain a biopsy of the depigmented lesions for further histopathological examination, including melanocytic immunohistochemistry, to distinguish between true vitiligo and vitiligo-like depigmentation. An argument favoring vitiligo is the comorbidity of Hashimoto’s disease, which directs towards a general tendency to develop autoimmune diseases. Arguments favoring a vitiligo-like depigmentation are the severity of the previous CLE lesions and the limitation to previously affected areas. Hydroxychloroquine might have contributed to depigmentation as its affinity for melanin may establish an interference with melanogenesis. Chloroquine-induced depigmentation of sun exposed areas in patients with ethnically dark, pigmented skin after months of treatment is a well-known phenomenon [16]. Our clinical report differs from that as there are, until now, no reports of hydroxychloroquine-induced depigmentation in fair skinned patients. The clinical picture in our patient with Fitzpatrick skin phototype II exceeds commonly seen postinflammatory hypopigmentation, which tends to resolve within weeks to months after effective treatment of the causative condition; although persisting lesions have been described in chronic discoid CLE and subacute CLE [17]. Aside from inflammatory pathways, CLE and vitiligo are alike as they carry a high burden of disease considering psychological distress and health-related impairment of quality of life [18, 19].

In summary, we present a case report of striking vitiligo-like depigmentation after an intense flare of subacute CLE and hydroxychloroquine treatment. We hereby aim to highlight shared inflammatory pathways of anti-epithelial and anti-melanocytic autoimmune skin reactions.
Table 1  Synopsis of common and diverging features of cutaneous lupus erythematosus and vitiligo. Proposed treatment modalities in former or active clinical trials are marked in italics.

|                            | Specific LE                              | Common features                      | Vitiligo                                 |
|-----------------------------|------------------------------------------|--------------------------------------|------------------------------------------|
| **Environmental factors**   | UV-radiation, Cigarette smoke, Drugs     | Oxidative stress, Psychological stress (anxiety), Mechanical stress (Koebner phenomenon), Drugs (e.g. immune-checkpoint-inhibitors, TNFα-inhibitors, topical imiquimod, anticonvulsants) | Exposure to phenolic chemicals, Viral infections, Drugs (e.g. BRAF-inhibitors, tyrosine kinase inhibitors) |
| **Genetics**                | TREX1 gene mutations as cause of monogenetic form of familial Chilblain LE | Polygenetic predisposition/familial association, Genetic variants of genes involved in innate and adaptive immune system (cell death, clearance of cell debris, antigen presentation, antibody production and immune regulation) | No described monogenetic forms, Association with different HLA-subtypes |
| **Antibodies**              | ~ 50 % antinuclear antibodies in chronic discoid cutaneous LE, ~ 70 % anti-SSA/~ 30 % anti-SSB antibodies in subacute cutaneous LE, ~ 80 % antinuclear/~ 30 % anti-dsDNA-antibodies in systemic LE | ~ 10–12 % antinuclear antibodies, ~ 10–15 % anti-thyroid antibodies (anti-thyroperoxidase, anti-thyroglobulin) | |
| **Etiopathology and cytokines** | Activation phase: epidermal danger signals lead to activation of pattern recognition receptors (e.g. TLR-7) and complement system, Late phase: production of autoantibodies; release of endogenous nucleic acids; keratinocytic chemokines | Effector phase: IFN-system activation, activation of cytotoxic T-Cells | Activation phase: melanocytic stress leads to activation of innate immune cells and IDECs; consecutive release of HSP70, IL1-β, IL6 and IL8 as early steps in T-cell recruitment |
| **Histopathology**          | Interface dermatitis and/or patchy lymphocytic inflammatory pattern (depending on subtype), Apoptotic/necroptotic keratinocytes (colloid bodies), Presence of pDCs as IFN-producers | | Apoptotic melanocytes as result of T-cell destruction, Perilesional areas may display a sparse perivascular lymphocytic infiltrate |
| **Clinical aspects**        | Female predisposition, Young adulthood, UV-exposed body sites (face, upper back, dorsal sides of extremities) | Association with other autoimmune diseases | No sexual predisposition, Childhood and young adulthood, Face, periorificial regions, arms, hands, intertriginous areas |
Table 1 Continued.

| Cutaneous LE | Vitiligo |
|--------------|----------|
| Specific features | Common features | Specific features |
| Therapeutic strategies | – Avoiding triggers: sunscreen, smoking cessation | – Topical corticosteroids | – Avoiding triggers: Antioxidants (e.g. vitamins) |
| – Anti-malarials (chloroquine, hydroxychloroquine, mepacrine) | – Anti-malarials (chloroquine, hydroxychloroquine, mepacrine) | – Conventional immunosuppression (e.g. corticosteroids, methotrexate etc.) | – Physical measures (e.g. narrow band ultraviolet B, PUVA, lasers, red light, micro needling, punch-grafting, split-skin grafts) |
| – Anti-inflammatory antibiotics (e.g. dapsone) | – Inhibition of JAK-STAT-signaling pathway topically or systemically (e.g. ruxolitinib as JAK1/2 inhibitor, statins as off-target STAT1-inhibitors) | – Biologics directed at B-cell effects (e.g. belimumab, rituximab) | – Covering measures (e.g. camouflage) |
| – Anti-inflammatory supplements (nicotinamide) | – Biologics directed at pDC effects (e.g. Anti-CD303 antibodies, Anti-LILRA4 antibodies) | – Physical measures (e.g. narrow band ultraviolet B, PUVA, lasers, red light, micro needling, punch-grafting, split-skin grafts) | – Stimulation of melanocytes (e.g. afamelanotide) |
| – Biologics directed at B-cell effects (e.g. belimumab, rituximab) | – Biologics directed at T-cell effects (e.g. activating Immune-checkpoint-antibodies) | – Physical measures (e.g. narrow band ultraviolet B, PUVA, lasers, red light, micro needling, punch-grafting, split-skin grafts) | – PDE4 inhibitors (e.g. apremilast) |
| – Biologics directed at pDC effects (e.g. Anti-CD303 antibodies, Anti-LILRA4 antibodies) | – Psychosomatic care | – PDE4 inhibitors (e.g. apremilast) | – Depigmentation for extensive disease (> 50 % body surface area) |

Abbr.: LE, Lupus erythematosus; TNFa, tumor necrosis factor alpha; UV, ultraviolet; BRAF, v-Raf murine sarcoma viral oncogene homolog B; TREX1, three prime repair exonuclease 1; HLA, human leukocyte antigen; anti-SSA/SSB, anti-Sjögren’s syndrome related antigen A/B; dsDNA, double-stranded deoxyribonucleic acid; TLR-7, toll-like receptor 7; IFN-γ, interferon-γ; IL, interleukin; IDECs, inflammatory dendritic epidermal cells; HSP70, heat shock protein 70; pDCs, plasmacytoid dendritic cells; LILRA4, leukocyte immunoglobulin-like receptor subfamily A member 4; JAK, Janus kinase; STAT, signal transducer and activator of transcription; PUVA, psoralene and ultraviolet-A; PDE4, phosphodiesterase-4.

Acknowledgment

We thank the patient for granting permission to publish this information.

Conflict of interest

The authors have been an advisor and/or received speakers’ honoraria or travel expense reimbursements and/or received grants and/or participated in clinical trials of the following companies:

D.N.: BMS, Novartis, GSK, Celgene, L’Oréal, Kyowa Kirin and MSD
C.B.: Novartis, L’Oréal
T.B.: None
J. W.: GSK, Novartis, Medac, Merck/Serono, Roche, Actelion, Pfizer, Spirig, ArrayBio, Biogen, Kyowa Kirin

Dennis Niebel, Christine Braegelmann, Thomas Bieber, Joerg Wenzel

Clinic for Dermatology and Allergy, University Hospital Bonn

Correspondence to

Dennis Niebel, MD
Clinic for Dermatology and Allergy
University Hospital Bonn
Venusberg-Campus 1
53127 Bonn, Germany
E-mail: dennis.niebel@ukbonn.de

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