Lupus Erythematosus Tumidus

A Neglected Subset of Cutaneous Lupus Erythematosus: Report of 40 Cases

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Background: Lupus erythematosus tumidus (LET) is characterized clinically by erythematous, succulent, edematous, nonscarring plaques in sun-exposed areas. Results of histological examination show perivascular and periadnexal lymphocytic infiltration and interstitial mucin deposition. The main differential diagnoses are polymorphous light eruption, Jessner’s lymphocytic infiltration of the skin, reticular erythematous mucinosis, and pseudolymphoma. Since its first description in 1930, LET has been documented rarely in the literature, and its clinical importance has not been fully appreciated.

Observations: We characterized 40 patients with clinical and histological features of LET observed at our department from 1984 through 1998. The onset of the disease clustered in summer because of sun exposure, and 28 (70%) of the patients showed a remarkable photosensitivity confirmed by results of provocative phototesting. A complete resolution of the skin lesions was seen after systemic therapy with antimalarials and, in some cases, with local corticosteroids or spontaneously without any treatment. In 4 (10%) of the patients, antinuclear antibodies were detected; however, there was no evidence of underlying systemic involvement in any of the patients.

Conclusions: Our data constitute the largest number of patients with LET collected until now. The clinical picture, extreme photosensitivity, histological findings, and effective treatment with antimalarials are so characteristic that LET should be considered as a separate entity and differentiated from other variants of cutaneous LE.

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LUPUS ERYTHEMATOSUS (LE) is an autoimmune disorder resulting from an interplay of genetic, environmental, and hormonal elements with a heterogeneous clinical expression extending from a localized cutaneous form to a life-threatening systemic form. In 1977, Gilham proposed a nomenclature for cutaneous manifestations of LE, focusing especially on the relationship between the various forms. Since then, several attempts have been made to improve on this system or to provide altogether new approaches for the classification of cutaneous LE.

See also page 1044

Lupus erythematosus tumidus (LET), a rare subset of chronic cutaneous LE (CCLE), was first mentioned by Gougerot and Burnier in 1930 in a description of 2 patients with erythematous, infiltrated, nonscarring plaques on the face. In the following years, 3 additional patients with similar skin lesions were described by the same authors; however, the next case reports of LET were not mentioned until 1965 in the German and the French literature. In 1984, a patient was presented in the Spanish literature who showed an unpredictable evolution of LET before it resolved completely without scarring or atrophy. In 1987 and 1988, Kind and Goerz reported LET as a clinical and histological variant of CCLE that is difficult to differentiate from polymorphous light eruption (PLE) and Jessner’s lymphocytic infiltration of the skin. In 1990, Goerz et al emphasized the extreme photosensitivity as a major characteristic feature of LET and detected a male predominance with the peak of onset from 41 through 50 years of age. In a further study, the correlation between photosensitivity and anti–Ro/SSA antibodies, as described for patients with subacute cutaneous lupus erythematosus (SCLE), was not noticed in patients with LET. Effective treatment of LET skin lesions with antimalarials was first mentioned by Kind et al in 1992. The same group reported interstitial mucin deposition as a further characteristic feature of LET and...
PATIENTS, MATERIALS, AND METHODS

PATIENTS

Forty white patients with erythematous, succulent, non-scarring, elevated plaques of variable extent over the face, upper part of the back and chest, shoulders, and extensor aspects of the arms were included in our study. This group represented 16% of the total population of about 250 patients seen at the Department of Dermatology, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany, from January 1, 1984, through December 31, 1998, consisting of about 95% white patients with cutaneous forms of LE. The clinical diagnosis was supported by results of histological examination of lesional skin biopsy specimens and by serological investigations and experimental reproduction of skin lesions by UV-A and/or UV-B irradiation.

SELECTION AND PREPARATION OF SKIN SPECIMENS

Skin biopsy specimens were taken from primary lesions of all 40 patients with untreated LET and also from 28 of the 40 patients with lesions induced by experimental phototesting using UV-A and/or UV-B irradiation. Histological features were evaluated by means of light microscopy of hematoxylin–eosin– and colloidal iron–stained specimens fixed in a 10% solution of formaldehyde. Direct immunofluorescence examination of biopsy specimens from lesional skin was performed in 5 patients following a standard technique.

PHOTOTESTING

The light sources used included a high-pressure metal halide lamp (340-440 nm) (UVASellsa 2000 unit; Sellsa Medizinische Geräte, Gevelsberg, Germany) for UV-A phototesting and a UV-800 unit lamp with fluorescent bulbs (285-350 nm) (Philips TL 20 W/12; Waldmann, Villingen/Schwenningen, Germany) for UV-B phototesting. Irradiation output was monitored by means of a UV radiometer (UVAMETER; Mutzhas, Munich, Germany) and UV spectrometer (Waldmann). Minimal erythema dose (MED), threshold dose for immediate pigment darkening (IPD), and minimal tanning dose (MTD) were determined as previously described.21,22 For the provocative phototesting, areas (4 × 5 cm) of uninvolved skin on the upper back were irradiated with single doses of 100 J/cm² UV-A and/or 1.5 MED UV-B, respectively, daily for 3 consecutive days. Test areas were evaluated until specific lesions appeared for up to 4 weeks after the last irradiation. Criteria for positive provocative phototest results required that induced lesions clinically resembled LE, histopathological findings were compatible with LE, and skin lesions developed slowly and persisted for several days or weeks in contrast to other photodermatoses such as PLE.19,23 None of the patients received any systemic medication during the testing period.

LABORATORY STUDIES

Antinuclear antibodies (ANAs) were assayed using a standard indirect immunofluorescence technique with commercially available HEp-2 cells (Bio-Rad SDP GmbH, Freiburg, Germany). With this assay technique, serum ANA titers of greater than 1:160 are clearly abnormal compared with those of healthy controls. Levels of antihistone antibodies (dsDNA) antibodies, anti–Ro(SSA), anti–La(SSB), –U1 RNP, –Scl 70, and –Jo 1 antibodies, and anti–cardiolipin antibodies (ACA [IgM and IgG]) as well as anti–neutrophil cytoplasmic antibodies (ANCA [protease 3 (PR3) and myeloperoxidase (MPO)]) were determined by means of standardized enzyme-linked immunosorbent assays (ELISA; DPC Biermann, Bad Nauheim, Germany). Total hemolytic complement (CH50) was measured using the photometer, and lupus anticoagulant was evaluated by kaolin clotting time (KCT). Levels of immunoglobulins (IgM, IgG, and IgA), complement components (C3 and C4), C-reactive protein (CRP), and rheumatoid factor (RF) were measured using standardized assay protocols with a nephelometer (Behring Diagnostics, Marburg, Germany).

STATISTICAL ANALYSIS

For sex distribution, patients with LET were compared with the control group of 214 patients with other forms of cutaneous LE observed at our department from January 1, 1984, through December 31, 1998, consisting of 66 male and 148 female patients. Fisher exact test was used to determine the significance. To assess whether the age at onset of LET differs significantly between male and female patients, t test was performed. Confidence intervals were determined at 95%, and P values less than .02 were considered significant.

RESULTS

EPIDEMIOLOGICAL FEATURES

In our study, we have analyzed 40 patients with characteristic clinical and histological features of LET among a total of about 250 patients with cutaneous forms of LE, constituting an incidence of 16%. Sex, age at onset, and duration of the disease at the time of the study are listed in Table 1. Twenty-two (55%) of the patients with LET were male and 18 (45%) were female, revealing a significant difference compared with the control group (P = .003, Fisher exact test). The mean age of the entire results of direct immunofluorescence staining as often being negative; however, there was no doubt about LET being a separate subset of CCLE.

During the past 15 years, we have investigated clinical, histological, photobiological, and laboratory features of 40 patients with LET. The clinical importance of this edematous, non-scarring, photosensitive type of CCLE as a distinct subset has been neglected in the literature and, since it has not always been considered as a separate entity, we suggest criteria to differentiate LET from PLE, Jessner’s lymphocytic infiltration of the skin, reticulate erythematous mucinosis (REM), pseudolymphoma, SCLE, and other variants of CCLE.
group, when reviewed for the study in 1999, was 44.8 years, with a range of 10 to 62 years, and the mean age at onset of the disease was 36.4 years, with a range of 9 months to 54 years (Table 1). The mean duration of the disease was 7.8 years, and the mean interval between onset of the disease and confirmation of the diagnosis was 4.9 years, ranging from several months to 30 years. There was no significant difference in disease duration between male and female patients with LET (P=.51, t test), but the onset of the disease seems to be earlier in male patients.

**CUTANEOUS MANIFESTATIONS**

The clinical picture, one of the major criteria of LET, is characterized by nonscarring, erythematous, succulent, urticarialike single or multiple plaques with no surface changes such as follicular plugging (Figure 1). They involve sun-exposed areas (eg, face, upper back, V area of the neck, extensor aspects of the arms, and shoulders); spare the knuckles, inner aspect of the arms, and axillae; and have never been detected below the waist (Figure 2). Once a lesion has developed, it can disappear spontaneously within a few days or weeks, even if the disease recurs chronically in patients with LET. In a few cases, there is a tendency of the skin lesions to coalesce in the periphery, producing a gyrate configuration, and erythematous, annular lesions develop on the cheeks and upper extremities of some patients, imitating the annular type of SCLE. In 2 of the 40 patients with LET, characteristic discoid LE (DLE) lesions had occurred in the course of their disease. However, other cutaneous manifestations such as hypopigmentation, mucous membrane ulcers, diffuse alopecia, livedo reticularis, or vasculitis have never been seen in any of the patients. None of the patients with LET showed evidence of systemic involvement or had 4 or more of the American Rheumatism Association (ARA) criteria for the diagnosis of systemic LE (SLE).24

**HISTOPATHOLOGICAL FINDINGS**

The primary and the experimentally UV-induced skin lesions demonstrated perivascular and periadnexal superficial and deep lymphocytic infiltration (Figure 3). The density of the infiltration differed from slight to moderate and, in some cases, scattered neutrophils were seen. All of the biopsy specimens showed a distinct subepidermal edema and mucin deposition between collagen bundles (Figure 4). However, epidermal involvement usually was not found, and smudging of the dermoepidermal junction was only occasionally detected. Hyperkeratosis, slight epidermal hyperplasia, and sunburn cells were observed in some of the UV-induced skin lesions.

**IMMUNOPATHOLOGIC FINDINGS**

As previously described,15 results of direct immunofluorescence in specimens from patients with LET have mostly been negative at the dermoepidermal junction or around the papillary and reticular dermal blood vessels. In our study, none of the 3 major immunoglobulin classes (IgG, IgM, and IgA) or complement components (C3 and C4) were identified in any specimen.

**PHOTOTESTING**

Provocative phototests according to a standardized protocol are helpful in the diagnosis of cutaneous LE and can be performed with repeated irradiation of 60 to 100 J/cm2 UV-A and/or 1.5 MED UV-B.21,22 The development of positive reactions of phototests in LE is considerably slower and persists longer than in other photodermatoses such as PLE.21,22,25 In contrast to previous observations, most of the patients with LET reacted to UV-A and UV-B irradiation, as found for other forms of cutaneous LE.19,23,25,26 A few days after UV exposure, erythema and itching developed, followed by characteristic morphologic skin lesions of LET with histological changes similar to those in primary lesions (Figure 5). Patients with LET had been found to be even more photosensitive than patients with SLE19 and, in our study, experimental phototesting revealed characteristic skin lesions in 28 (70%) of the patients; 10 (56%) of the 18 tested patients reacted to UV-A and UV-B irradiation, 16 (40%) of the 40 patients to UV-A only, and 15 (38%) of the 40 patients to UV-B only. Twenty (50%) of the 40 patients were aware of an adverse effect of sunlight on their disease, and 15 (75%) of them showed pathologic test reactions. Pathologic test reactions were also induced in 12 (60%) of those patients who denied any effect of sun exposure on their disease.

**LABORATORY FEATURES**

Laboratory tests that were performed in all 40 patients with LET revealed ANAs with a titer of greater than 1:160 in 4 (10%) of the patients. The ANA fluorescence pattern was finely granular in all except 1 case, where it was homogeneous. Anti–Ro/SSA and –La/SSB antibodies were detected in 2 (5%) of the patients with ANAs, and dsDNA antibodies were present at a low serum concentration in only 1 patient (3%). Anti–U1RNP, –Sm, –ScI 70, or –Jo 1 antibodies were not detected in any case. Anti–cardiolipin antibodies were temporarily positive at a low serum titer in 4 (10%) of the patients, but findings for KCT and ANCA were negative in all patients. Decreased C3 levels occurred temporarily in 11 (28%) of the patients and decreased C4 levels were detected in only 2 (5%). An elevated RF was present temporarily in 2 patients (5%), and findings for CRP were positive in 12 (30%). Levels of IgG and IgM were elevated in 3 patients (8%) and IgA in 4 (10%), whereas findings for CH50
were negative in all of the patients. Only 1 patient (3%) showed a transient leukopenia, and 3 (8%) disclosed a thrombopenia. A mildly elevated creatinine level from 97.3 to 141.5 µmol/L (reference value, 88.4 µmol/L) (1.1-1.6 mg/dL [reference value, 1.0 mg/dL]) was transiently found in 5 patients (12%), but a pathologic creatinine clearance was not detected.

COURSE OF THE DISEASE AND THERAPY

One of the patients had had LET for more than 30 years at presentation in our clinic; however, most patients had been affected for less than 6 years (Table 1). The youngest patient was aged 9 months at initial diagnosis and had already had recurrent skin lesions for 10 years.27 The clinical features observed during exacerbations of the disease activity in individual patients with LET occurred in most of the cases in summer due to sun exposure, and some patients reported that even after sitting behind glass windows, their skin disease had worsened, indicating that long-wavelength UV light is capable of activating LET. None of the 40 patients had a history of drug-induced LET in our study after up to 15 years of follow-up. Since the face is most often affected, LET obviously has a significant cosmetic implication. A complete resolution of the skin lesions was seen in 18 patients (45%) who had received only topical corticosteroids or sunscreens with a sun protection factor of 15 or greater. Twenty-two patients (55%) who had failed to respond to this regimen were treated with antimalarials. Chloroquine phosphate was successfully used in a daily dose of 3.5 to 4.0 mg/kg per day, and a complete resolution of the skin lesions was seen mostly after 4 to 6 weeks in the treated patients. In 3 patients (8%) who did not respond to this treatment, hydroxychloroquine sulfate was successfully used in a daily dose of 6.0 to 6.5 mg/kg per day. All patients receiving antimalarials for several months or years underwent laboratory studies, including complete blood cell counts and renal and liver function tests, before the onset of therapy and every 4 to 6 weeks thereafter, as well as ophthalmologic examinations (eg, fundoscopy, perimetry, color vision, and electro-oculography) every 6 months. Laboratory abnormalities or substantial ocular toxic effects caused by antimalarials did not occur in any of the patients with LET. Because of the rapid and effec-
tive improvement of the skin lesions after treatment with antimalarials, systemic corticosteroids or immunosuppressants were temporarily necessary in only 2 patients.

**COMMENT**

In this report, we have analyzed the clinical, histological, photobiological, and laboratory features of 40 patients with LET. Although the patients are clinically identified by a characteristic type of skin lesion, LET has been reported previously in the literature in only a few cases.6-15,19,20,27-31 This might be because other authors have not considered LET as an entity separate from other variants of CCLE and, therefore, it is quite likely that skin lesions described under different designations, such as “urticarial plaque lupus erythematosus,” represent the same disease.30 Since some skin conditions share a number of similar features (Table 2), a correct diagnosis demands attention to rather subtle details and appreciation of the characteristic signs as well as the course of the disease (Table 3). Nearly all the case reports of LET in the literature are published by European countries, especially Germany and France, indicating that many more white patients are seen. However, in our opinion, there is no doubt about LET being a separate entity that has been neglected in the literature since first being described in 1930.

In contrast to different forms of CCLE or SCLE, a slight male predominance was detected in our study; however, this was not as prominent as previously reported for LET.16 The mean age at onset of the disease is nearly the same as described for DLE; therefore, compared with SCLE or SLE, patients with LET are older when the disease begins.44 Skin lesions of LET had already developed in a male patient when he was 9 months of age.27 Since several patients whom we had observed for up to 15 years had shown no recurrence after local or systemic treatment, the disease might spontaneously resolve; however, this would need to be confirmed by long-term investigations in a greater number of patients. In several aspects, the cutaneous manifestations of LET differ from other variants of CCLE.28-30 Scarring, the hallmark of DLE, does not occur in LET, even in patients with recurrent LET skin lesions at the same site for many years, and epidermal atrophy has not developed in any
case. Follicular plugging and adherent hyperkeratotic scaling, which are also features of DLE, have not been seen in any of the patients. Hypopigmentation, frequently evident in patients with SCLE after the active phase with erythema and scaling, has never been detected in patients with LET. Following some of the patients had presented with annular skin lesions, there might be a possibility of development of annular erythema associated with Sjogren syndrome; however, this rare entity has mostly been reported for Asian patients. Histological evaluation of skin lesions is necessary to confirm the diagnosis of LET, and, therefore, it represents one of the major criteria of this disease (Table 3). In contrast to SCLE and DLE, follicular hyperkeratosis, epidermal atrophy, vacuolar degeneration, and thickening of the basement membrane zone usually are not found. The perivascular and periadnexal infiltrate is composed of lymphocytes and, in some cases, scattered neutrophils are seen. In all lesions of LET, a distinct subepidermal edema is present, and moderate to copious interstitial mucin deposition is detected with the use of colloidal iron staining. As previously described, results of direct immunofluorescence staining of lesional skin specimens of LET have mostly been negative for immunoglobulin or complement components. In contrast, early reports suggested that more than 90% of DLE lesions have granular, often thick, deposition of multiple immunoreactants at the dermoeidermal junction, and that approximately 60% of SCLE lesions show immune deposits in a bandlike pattern at the dermoeidermal junction or in a dustlike pattern scattered through the epidermis and the cellular infiltrates. However, the diagnosis-
tic significance of immunohistological examination has been the subject of much controversy during recent years. Since immune deposits are not specific for LE (similar deposits can be found in nonlesional and sun-damaged skin or in other skin diseases), considerable caution must be taken when interpreting the results of immunopathologic findings in lesional and nonlesional skin specimens.

Photosensitivity, one of the 11 ARA criteria for the diagnosis of SLE, was investigated in all of the 40 patients with LET by means of experimental reproduction of skin lesions after UV radiation. Because of the latency period in development of positive phototest reactions, it may be difficult for patients to link sun exposure with their skin lesions. Interestingly, in our study, there was a positive history for UV sensitivity in 20 patients (50%) and positive phototest reactions in 15 (75%) of these patients. As previously described, patients with LET were even more photosensitive than those with SCLE or DLE. In contrast to the studies by Kind et al in 1993, our data showed a positive result of provocative phototesting in all 4 patients (10%) with ANAs, and all 6 patients (15%) with moderate ANA titers also had development of skin lesions after UV radiation. Antibodies to the nucleoprotein antigens Ro/SSA, and sometimes also La/SSB, have been described to be highly associated with photosensitivity in SCLE, SLE, and neonatal LE (NLE). In NLE, the percentage of patients with antibodies specific for anti–Ro/SSA antibodies approaches 100%, and in SCLE, the association varies from a minority of patients to 90% or more because of differences between the diagnostic criteria used at various institutions and because of varying methods for detecting anti–Ro/SSA antibodies.

In our study, none of the 40 patients with LET fulfilled 4 or more ARA or European Academy of Dermatology and Venerology (EADV) criteria. Although joint symptoms occurred temporarily in some of the patients, no signs of inflammatory joint disease or rheumatoid arthritis were detected in any patients. Further systemic manifestations, such as renal, central nervous system, or lung involvement, have not yet manifested in any of the 40 patients during our study after up to 15 years. In contrast, Kind and Goerz have reported a rare but possible systemic involvement in patients with LET, but no specific manifestations have been documented.

Lupus erythematosus tumidus bears striking similarities to PLE, Jessner’s lymphocytic infiltration of the
skin, REM, and pseudolymphoma (Table 2). Polymorphous light eruption is a frequent UV-induced dermatitis of papular, papulovesicular, or plaquetlike appearance. The skin manifestations are monomorphous in the individual patient, and the disease is most common from March through June in geographic areas with a temperate climate, but can appear at any time of the year in tourists traveling to sunny areas. Young women are most often affected, and there is no restriction to race or age. The clinical distinction between PLE and LET can be difficult; however, LET shows a much more delayed reaction after sun exposure, and healing of skin lesions takes much longer, even when sun exposure is avoided and a sun block is applied daily. In particular, desensitization phototherapy or photochemotherapy are the most effective forms of preventive treatment in PLE, nevertheless, the uncertain long-term risks have to be weighed against the benign and self-limited disease.

In Jessner’s lymphocytic infiltration of the skin, the development of asymptomatic, papulonodular, nonscarring lesions classically involving the face is unrelated to UV exposure in most of the patients. Male patients are predominantly affected, and there is no sign of systemic involvement. In contrast to LET, histological features of Jessner’s lymphocytic infiltration of the skin show no interstitial mucin deposition, but varying numbers of plasma cells may be present. However, Jessner’s lymphocytic infiltration of the skin is not always considered as a specific disease entity, and some of the cases described in the literature might, in our opinion, represent LET. There is only one study to date comparing Jessner’s lymphocytic infiltration of the skin with LET.

Reticular erythematous mucinosis is also considered to be a variant of DLE or LET by some authors, especially because REM can be induced by sun exposure and antimalarials have been reported as the most effective therapy. In contrast to LET, young to middle-aged women are mostly affected, and the skin lesions, ranging from erythematous, indurated papules to reticulated, macular erythema, are mainly localized on the central chest or upper back. Histological features of REM show a mild to dense perivascular infiltrate of lymphocytes with abundant mucin deposition in the dermis. Furthermore, pseudolymphoma also can simulate LET clinically; however, in most of the cases, histological evaluation shows a top-heavy, usually wedge-shaped infiltrate of small lymphocytes as well as plasma cells and eosinophils.

In summary, LET presents a rare, but distinct, subset of CACLE with characteristic clinical features requiring correlation with histological, photobiological, and laboratory findings, since, taken in isolation, other diagnoses can be indicated. Our data emphasize the importance of defining LET as a separate entity and demonstrate that this disease has been neglected in the literature since first described in 1930.

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