The Egyptian Rheumatologist 42 (2020) 245–250

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

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

Lupus erythematosus tumidus (LET) with autoimmune thyroid dysfunction (AITD) as the first presentation of systemic lupus erythematosus: A case report and review of the literature

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ARTICLE INFO

Article history:
Received 30 January 2020
Accepted 1 February 2020
Available online 18 February 2020

Keywords:
Systemic lupus erythematosus
Cutaneous lupus erythematosus
Lupus erythematosus tumidus
Hypothyroidism
Autoimmune thyroid dysfunction
Discoid lupus erythematosus

ABSTRACT

Introduction: Lupus erythematosus tumidus (LET) is a rare cutaneous manifestation especially as a first presentation of systemic lupus erythematosus (SLE). Autoimmune thyroid dysfunction (AITD) may be associated with SLE but rarely at initial presentation, and its diagnosis may be delayed.

Case report: A 29 year old male presented to Tishreen Hospital in Damascus with a three-year history of recurrent cellulitis-like lesions on the face, and more recently, he developed similar lesions on the trunk and the chest, in addition to the development of peripheral and scrotal edema, constipation, xeroderma, hair loss, musculoskeletal pain and depression. Laboratory investigations revealed: leukopenia, anaemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Immunological tests identified the positive anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), anti Ro/SSA, anti La/SSB antibodies. Additionally, there was consumed complement C3, elevated thyroid stimulating hormone (TSH), thyroid hormones decreased free T3 and T4 and anti-thyroid peroxidase (anti-TPO) antibody was positive. Skin biopsy from the cheek plaque suggested the presence of LET and revealed slight hyperkeratosis; actinic elastosis, telangiectasia and edema of the papillary dermis; deep dermis perivascular and periadnexal inflammatory infiltrates with karyorrhexis of the lymphocytes and dermis edema between strands of collagen. The patient fulfilled the SLE classification criteria and consequently, methylprednisolone, azathioprine, hydroxychloroquine, levothyroxine were introduced with dramatic improvement.

Conclusion: LET is a rare cutaneous lupus-specific lesion that may be associated with SLE. AITD, hypothyroidism in particular, could be an initial presentation of SLE. Increased awareness and early diagnosis of such clinical presentations may improve patient outcomes.

1. Introduction

Lupus erythematosus (LE) is a chronic inflammatory autoimmune disease that manifests in cutaneous and systemic forms [1]. It occurs more frequently in childbearing females with a female to male ratio up to 13:1 [2]. Serositis, discoid lesions and subacute cutaneous lupus are more frequently seen in men [3]. Systemic lupus erythematosus (SLE) is a multisystemic disorder [2] and cutaneous manifestations are important features that occur in 75–85% of cases [1]. Skin involvement has a variable course ranging from mild to severe and affects patient's daily activities and quality of life [1]. Skin manifestations were classified as lupus-specific and non-specific according to histopathologic criteria [4]. Lupus non-specific cutaneous manifestations could also occur in other diseases such as Raynaud's syndrome, periungual telangiectasia, alopecia, livedo racemosa and leukocytoclastic vasculitis [4]. Lupus-specific skin manifestations are classified into four cutaneous LE (CLE) subtypes: acute (ACLE), subacute (SCLE), chronic (CCLE) and intermittent (ICLE) [4]. The ACLE disease is highly photosensitive and can result in generalized or localized non-scaring eruptions while the histopathology shows dermatitis and minimal vacuolization of the basement membrane. Malar erythema is the most common localized form of this subtype [5]. SCLE is a photosensitive, non-scaring eruption with annular or psoriasiform lesions. Its histopathology shows dermatitis and vacuolar

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
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https://doi.org/10.1016/j.ejr.2020.02.002
1110-1164/

alteration of keratinocytes and some perivascular and periadnexal mononuclear infiltration [1]. CCLE has three forms: Chilblain, profundus and discoid LE (DLE) which is the most common. DLE is characterized by discoid indurated scaly lesions that heal with scarring. CCLE histopathology shows hyperkeratosis, dermatitis, thickening of basement membrane, while the inflammatory infiltration is denser than that in ACLE and SCLE [1,6].

Lupus erythematosus tumidus (LET) is an ICLE characterized by urticarial-like erythematous papules and plaques which are usually found on the face, upper back, and chest [7–9]. The course of LET is benign, and lesions may persist for months and resolve without hyper or hypopigmentation [10]. ICLE histopathology shows perivascular and periadnexal lymphocyte infiltration [1]. Multiple cutaneous lesions could be seen in the same patient [11,12]. However, only a few cases of an association of LET and SLE have been reported [11,13–17].

The association of SLE with other autoimmune diseases, such as autoimmune thyroid dysfunction (AITD) has been extensively studied [18,19]. While such association was considered controversial, recent meta-analyses become more supportive of it [20,21]. This case report presents a male SLE patient initially presenting with LET and later exhibited AITD.

2. Case presentation

A 29-year-old male patient presented to the oral and maxillofacial surgery department in a public hospital, with a three-year history of recurrent swelling, redness and warmth in his left cheek which resolved spontaneously without any treatment. Five months before admission, the lesion became persistent and was associated with left eyelid edema and fever (39°) (Fig. 1.A). The patient was initially diagnosed with periodontal abscess and cellulitis and the suspected tooth was surgically extracted. The patient was given a course of systemic antibiotics post- surgery. However, 25 days after the procedure, there was no improvement despite changing his antibiotics course. One month preceding the admission, he developed similar lesions on the chest and upper trunk which were fixed erythematous plaques, In addition to, he developed moderate dyspnea, chest pain, severe constipation, peripheral edema, xeroderma and hair loss, along with depression, severe fatigue and muscle ache. Further blood tests demonstrated a decrease in hemoglobin content, albumin and white blood cell (WBC) count, coupled with an increase in the erythrocyte sedimentation rate (ESR) (Table 1). Following consultation of a rheumatologist, the patient was admitted to the Rheumatology Department, Tishreen Hospital, Damascus, Syria.

On examination, there was firm erythematous plaque on the cheek, trunk and the upper part of the chest wall (Fig. 2), in addition to severe scrotal and peripheral edema and bradyphemia (abnormally slow speech). Immunological tests identified positive antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid (anti-dsDNA), anti-Sjögren's-syndrome-related antigen A (anti-SSA/Ro) and B (anti-SSB/La) antibodies, consumed complement 3 (C3) level and normal C4. Computed tomography (CT) chest-abdomen-pelvis revealed bilateral pleural effusion, slight pericardial effusion and enlarged lymph nodes around the celiac

Table 1
Laboratory findings in the male case with lupus erythematosus tumidus (LET) and systemic lupus erythematosus (SLE).

Lab. test	Value
Hb	9.6 g/dl
WBC	3790 C/μL
ESR	119 mm/1st hr
Albumin	29.2 g/L
24hr urine protein	Normal
ANA	Positive 1/320
Anti-dsDNA	Positive 1/160
HBV and HCV	Negative
Anti-SSA/Ro	Positive
Anti-SSB/La	Positive
C3	50 mg/dl
C4	22.5 mg/dl
TSH	90.95 μU/ml
FT3	<0.88 pg/ml
FT4	<0.33 ng/dl
Anti-TPO	59 units/ml

Hb: hemoglobin, WBC: white blood cell, ESR: erythrocyte sedimentation rate, ANA: antinuclear antibody, anti-dsDNA: anti-double stranded deaoxyribonucleic acid, HBV and HCV: hepatitis B and C virus, anti-SS: anti-Sjögren's-syndrome-related antigen, C: complement, TSH: thyroid stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, anti-TPO: anti-thyroid peroxidase. Normal values of the studied laboratory investigations are: Hb 13.7–16.7 g/dl, WBC count 4.5–11 × 10^3/cm, albumin 35–45 g/dl, C3 75–150 mg/dl, C4 21–54 mg/dl, TSH 0.4–4 μU/ml, FT3 2.4–4.2 pg/ml, FT4 0.8–1.8 ng/dl, anti-TPO > 35 U/ml.

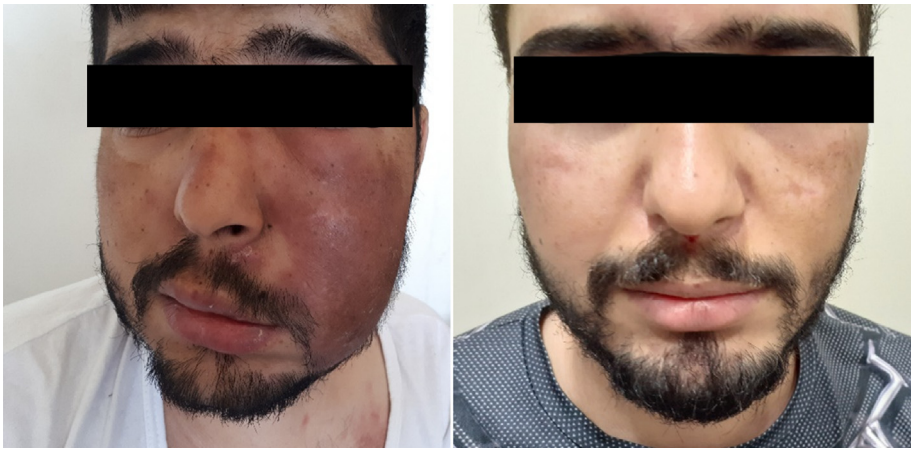

Fig. 1. A 29 year old Syrian male patient with 3 year history of recurrent swelling, redness and warmth in his left cheek, left eyelid edema and fever (39°) later diagnosed as lupus erythematosus tumidus (LET) and autoimmune thyroid dysfunction (AITD) as the initial presentation of systemic lupus erythematosus (A) and after 5 months of treatment with a maintenance dose of prednisolone (7.5 mg/day), azathioprine (100 mg/day) and hydroxychloroquine (200 mg/day) the patient is symptom-free with no signs of relapse (B).

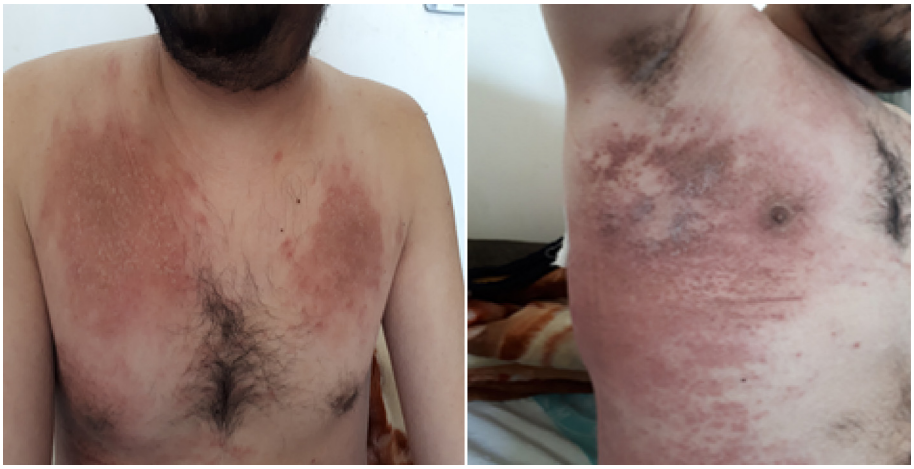

Fig. 2. A 29 year old Syrian male patient on examination showing erythematous plaque on the trunk and the upper part of the chest wall as well as the cheek and later diagnosed as lupus erythematosus tumidus (LET) and autoimmune thyroid dysfunction (AITD) as the initial presentation of systemic lupus erythematosus.

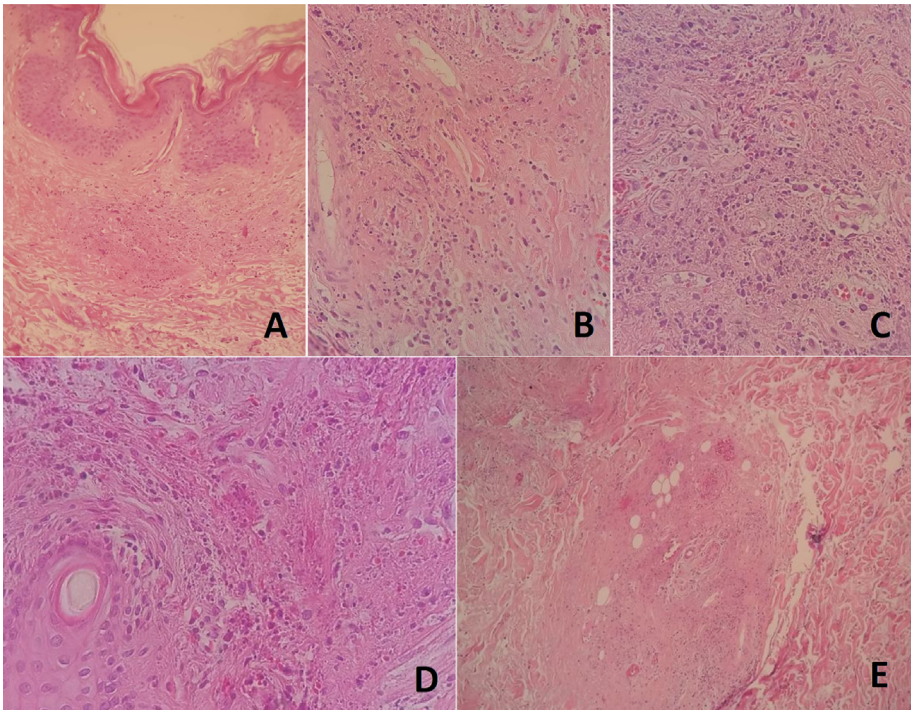

Fig. 3. Skin biopsy histopathology showing slight hyperkeratosis in the epidermis, and edema between strands of collagen in the deep dermis (A), perivascular lymphocyte infiltration with karyorrhexis (B), inflammatory infiltration in the dermis (C), perivascular and periadnexal inflammatory infiltration (D) and edema and inflammatory infiltration in the deep dermis (E) in a 29 year old Syrian male patient with lupus erythematosus tumidus (LET) and autoimmune thyroid dysfunction (AITD) as the first presentation of systemic lupus erythematosus.

trunk. Skin biopsy from the cheek plaque revealed slight hyperkeratosis; the papillary dermis revealed actinic elastosis, telangiectasia, edema; the deep dermis showed perivascular and periadnexal infiltrate, composed of chronic inflammatory cells (lymphocytes and plasma cells) with karyorrhexis of the lymphocytes and dermis edema between strands of collagen (Fig. 3).

The patient fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [22] as there was serositis, leucopenia/lymphopenia, positive ANA and anti-dsDNA, in addition to the cutaneous lesions.

Because of the increase in pericardial effusion and progressive dyspnea, the patient was given pulse methylprednisolone (1 g/day for 3 days) followed by oral prednisolone (40 mg/day) which was tapered gradually to a maintenance dose of 7.5 mg/day; in addition to hydroxychloroquine (400 mg/day) and azathioprine (150 mg/day). The patient's symptoms including, fever and skin lesions gradually improved following treatment, along with a significant improvement of the constitutional symptoms and a decrease in ESR and CRP. However, scrotal and peripheral edema, bradyphemia and depression have progressed, promoting a hypothyroidism suspicion. Therefore, the levels of thyroid stimulating hormone (TSH) (thyrotropin), free thyroxine (FT4), free triiodothyronine (FT3) were measured and anti-thyroid peroxidase (TPO Ab) was tested. TSH level was found to be elevated, while FT4 and FT3 levels were reduced, and TPO antibodies were identified (Table 1). Following the administration of daily

levothyroxine (100 mcg), the patient exhibited significant clinical improvement.

Finally, the patient was discharged with a diagnosis of SLE, LET and severe AITD. In the follow up period, after 5 months of treatment with a maintenance dose of prednisolone (7.5 mg/day), azathioprine (100 mg/day) and hydroxychloroquine (200 mg/day), the patient is symptom-free with no signs of relapse (Fig. 1B).

3. Discussion

The current case reports LET presenting by recurrent erythematous, firm plaques on the cheek, trunk and upper chest wall as an initial presentation of SLE and associated with AITD. Initially, the lesion on the face was associated with high-grade fever, along with constitutional symptoms. This mislead the diagnosis, as the patient was considered to have recurrent periodontal abscess with cellulitis, and treated with antibiotics with no improvement. SLE was only suspected due to the presence of dyspnea, chest pain, depression, hair loss and leukopenia. In addition, immunological tests revealed a positive ANA and anti-dsDNA with the findings of the skin biopsy later supporting the diagnosis. Treatment with steroids, azathioprine, and hydroxychloroquine was immediately introduced and resulted in overall improvements in patient symptoms, with the exception of generalized pitting-edema of the extremities and scrotum, fatigue, bradyphemia, and the depression. Therefore, a concomitant hypothyroidism diagnosis was suspected, and an AITD confirmed by laboratory tests. Significant improvement in hypothyroidism symptoms was observed following treatment with daily levothyroxine. Initially, SLE Symptoms masked the clinical manifestations of hypothyroidism, thus hypothyroidism was not the first differential diagnosis in the present case.

On searching the medical literature, LET was first reported in 1930 by *Gourget and Burnier* in two patients with infiltrated non-scarring erythematous plaques on the face [10]. The prevalence and incidence of LET is still lacking, and is rarely associated with SLE [7]. However, LET is often associated with other forms of CCLE such as DLE [17,23]. LET has a male predominance with high photosensitivity, and the lesions mostly disappear without scarring [1]. It occurs more frequently as a distinct disease compared with cases associated with SLE [4,24]. Furthermore, only a few cases have been reported with LET as the first presentation of SLE. The limited number of cases with an association of LET and SLE [11,13–17] as well as the present case are listed in Table 2. In some cases, LET was the key that lead to the diagnosis of SLE, while in others, LET preceded SLE for variant periods of time, ranging from months to years [25]. This may point to the clinical importance to check on patients who first present with isolated LET, as they may develop SLE later.

It is important to distinguish LET from other conditions that may be confused with this case, such as polymorphous light erup-

Table 2
Case reports of the association between systemic lupus erythematosus (SLE) and lupus erythematosus tumidus (LET) and the present case.

Case Report	Sex	Age (years)	LET lesions (site)	Country	Year
Wozniacka et al. [11]	F	25	Face, Back, Arms	Poland	2004
Jolly et al. [17]	F	38	Back	USA	2004
Chogle et al. [16]	F	58	Back, Neck	India	2011
Stitt R et al. [15]	F	22	Face	Hawaii	2014
Fernandes et al. [14]	F	12	Face	Portugal	2019
Lerman et al. [13]	M	27	Head (alopecia)	USA	2019
	M	31			
This case	M	29	Cheek, Chest, Trunk	Syria	2020

LET: lupus erythematosus tumidus, SLE: systemic lupus erythematosus

Table 3
Studies of the association between systemic lupus erythematosus (SLE) and thyroid disorders.

Study	SLE Patients (n°)	Thyroid disorder	Frequency (%)	Country	Year
Chan et al. [32]	69	Thyroid dysfunction	(24.6)		2001
		Anti-TPO positive	(23.2)	England	
		Hypothyroidism	(17.4)		
		- *clinical*	(4.4)		
		- *subclinical*	(13)		
Shahin et al. [31]	45	Primary hypothyroidism	(4.4)		2002
		Secondary hypothyroidism	(13.3)	Egypt	
		Anti-TgAb	(18.5)		
		Antimicrosomal antibodies	(95.6)		
Al-Awadhi et al. [33]	60	Subclinical hypothyroidism	(13.3)		2008
		Overt hypothyroidism	(8.3)	Kuwait	
		Euthyroid sick syndrome	(16.7)		
Al Saleh et al. [34]	110	Hypothyroidism	(13.7)	United Arab Emirates	2008
		Anti-TgAb positive	(14.6)		
		Anti-TPO positive	(25.6)		
		Positive both antibodies	(13.7)		
Viggiano et al. [35]	106	Subclinical hypothyroidism	(11)	Brazil	2008
		Clinical hypothyroidism	(13)		
Franco et al. [36]	376	Autoimmune hypothyroidism	(12)		2015
		Euthyroid/elevated anti-TPO	(21)	Colombia	
		Euthyroid/elevated anti-TgAb	(10)		
Ong et al. [37]	189	AITD	(6.3)	Malaysia	2015
		Hypothyroidism	(3.7)		

SLE: systemic lupus erythematosus, anti-TPO: anti-thyroid peroxidase, anti-TgAb: antithroglobulin antibody, AITD: autoimmune thyroid disease.

tions, pseudolymphoma, and Jessener lymphocytic infiltration of the skin [26,27]. Lesion biopsy is the standard of care diagnostic tool to confirm LET diagnosis. Histopathologically, LET is characterized by periadnexal and perivascular lymphocytic infiltration, in addition to subepidermal mucin deposition between collagen fibers, slight epidermal hyperkeratosis and edema in the papillary dermis [5].

The association of SLE and AITD has been notably reported and evidenced [28,29]. It has been reported that SLE is significantly associated with a higher frequency of both clinical and subclinical hypothyroidism [20]. Higher titers of thyroglobulin antibodies (Tg Ab) and TPO Ab were found in SLE patients with Hashimoto's Thyroiditis [30]. However, there is a necessity to conduct further studies to validate the link between the two conditions. Studies [31–37] on this association are presented in Table 3.

Epidemiologic data suggest a key role for genetic susceptibility between SLE and AITD, as the two diseases share similar genetic predisposition, which has been suggested as a possible explanation of their link [38,39]. Some of these co-predisposing genes are in the 5q14.3-q15 loci, R620W polymorphism of the protein tyrosine phosphatase PTPN22, in addition to the role of HLAB8 and DR [37,40]. These genes interact with cytokines and chemokines, and are triggered by environmental factors, leading to the breakdown of self tolerance and potential development of AITD; Hashimoto thyroiditis and Grave disease [21].Up till now; there is no definite recommendation to screen for hypothyroidism in SLE patients.

In conclusion: LET is a rare cutaneous lupus-specific lesion that may be associated with SLE. AITD, hypothyroidism in particular, could also be an initial presentation of SLE. Increased awareness and early diagnosis of such clinical presentations may improve patient outcomes.

Acknowledgement

Authors are grateful for Dr. Wisam Assad and Dr. Ahmad Darweesh for their assistance in the histopathogical section, and Dr. Ammar Suleiman, Head of Medical Services Institution, Dr Moufid Drawich for their support and advice.

Conflict of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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