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ORIGINAL ARTICLE

Pulmonary involvement in early systemic lupus erythematosus

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KEYWORDS

Lung involvement;
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Abstract *Aim of the work:* SLE is an autoimmune disease characterized by a variety of clinical and laboratory abnormalities. It may affect many organs and pulmonary involvement is a common finding in SLE. The purpose of this study was to disclose the pulmonary involvement in early SLE patients not more than 2 years of disease duration using the computed tomography (CT) as well as the pulmonary function tests as ways of pulmonary involvement assessment.

Patients and methods: Forty-two patients aged 29 ± 12.5 with early SLE not more than 2 years of disease duration were recruited for the study. All patients were assessed clinically for their SLE with BILAG which was utilized for disease activity determination.

Results: Nine and half percent of our patients were found to be clinically involved by ILD, where 28.6% have abnormal HRCT finding, 26.2% with abnormal PFT. Variants that were associated with an abnormal forced vital capacity FVC < 80% in a significant manner were: smoking, long disease duration, self-reported pulmonary symptoms (p 0.001), BILAG global score (p 0.006), Anti dsDNA (p 0.001), Antiphospholipid (IgM or IgG) (p 0.01), anti Sm (p 0.002), anti-RNP (p 0.005), HRCT abnormalities (p 0.001), current medication of steroid (any dose) (p 0.005), immunomodulator therapy (p 0.002), and Rituximab therapy (p 0.001).

Conclusions: ILD occurs as early as in the first 2 years in the course of SLE patients. There was a clear predilection of ILD with certain variables in our cohort of patients.

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1. Introduction

Systemic lupus erythematosus (SLE) is a connective tissue disease characterized by the formation of autoantibodies and immune complexes [1–3]. It is an autoimmune disease characterized by a variety of clinical and laboratory abnormalities. It may affect many organs and pulmonary involvement is a common finding in SLE [4] (see Figs. 1 and 2).

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Pleuro-pulmonary manifestations are present in almost half of the patients during the disease course and may be the presenting symptoms in 4–5% of patients with SLE. Complications directly associated to the disease include pleuritis with or without pleural effusion, alveolitis, interstitial lung disease, lupus pneumonitis, pulmonary hemorrhage, pulmonary arterial hypertension, and pulmonary thromboembolic disease. Complications due to secondary causes include pleuro-pulmonary manifestations of cardiac and renal failure, atelectasis due to diaphragmatic dysfunction, opportunistic pneumonia, and drug toxicity [5–7].

High resolution computed tomography (HRCT) and pulmonary function tests (PFTs) are the most frequent investigation tools used for the detection and follow up of lung involvement in SLE [8,9]. HRCT is more sensitive than PFTs or chest X-ray (CXR) in the evaluation of pleuropulmonary disease in SLE [10].

Many articles have studied the lung involvement in systemic lupus erythematosus, yet sparse works explore how early the pulmonary involvement happens in the natural course of SLE.

The aim of the present study is to reveal the pulmonary involvement in early systemic lupus erythematosus patients with not more than 2 years of disease duration using HRCT together with PFTs as tools of pulmonary involvement assessment.

2. Patients and methods

Forty-two patients with early SLE not more than 2 years of disease duration who were fulfilling the American College of Rheumatology (ACR) classification criteria for SLE [11] were recruited for the study in the period from January 2010 to January 2013.

Disease duration at enrollment was defined as duration from the date of physician diagnosis until the date at first study visit. An informed consent was obtained for every patient participating. Mean duration of disease was 20 ± 4 months. Patients with a previous diagnosis of another connective tissue disorder which may associate SLE such as rheumatoid arthritis, primary Sjögren's syndrome, mixed connective tissue disease, systemic sclerosis, antiphospholipid antibody syndrome or idiopathic inflammatory myositis were excluded from this study. Presence or absence of pulmonary symptoms is not considered as exclusion or inclusion criteria for patient's enrollment in the study. The study was approved by the local ethics committee of the hospital (Al Ahsa hospital, Al-Ahsa, Eastern District of KSA) and written consents were provided by the included patients.

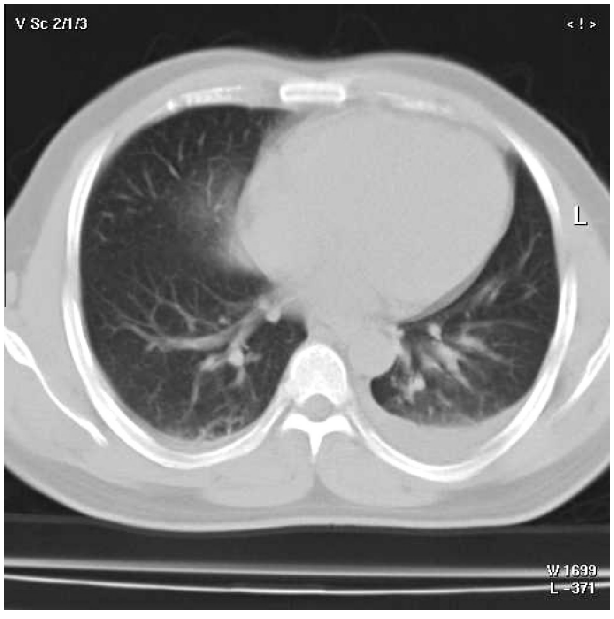

Figure 1 HRCT of lung window of lower lung zone in an early SLE patient revealed: left pleural effusion, bilateral basal fine subpulmonary thin septation with minimal small cystic changes.

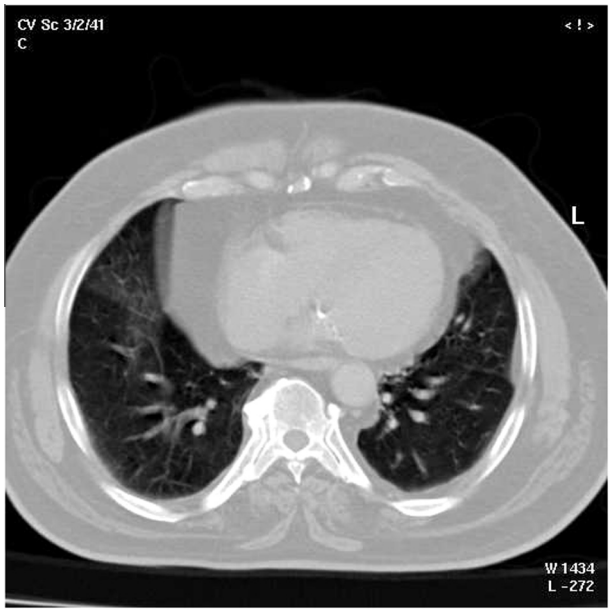

Figure 2 HRCT of lung window of lower lung zone in an early SLE patient revealed: ground glass appearance of anterior segment of right lower lobe.

2.1. Clinical assessment

Thorough history taking and full clinical examination were done for all patients including medication history. All the patients were subjected to overall clinical assessment and disease activity assessment was performed using the BILAG (British Isles Lupus Assessment Group) disease activity index [12]. It distinguishes activity in 8 organs or systems namely general, mucocutaneous, central nervous system, musculoskeletal, cardio-vascular system/respiratory, vasculitis, renal and hematological systems. It provides an accurate means of grading disease activity from the "most active" to "no evidence of disease activity currently". Patients are classified to 5 grades: A = 9 points, B = 3 points, C = 1 point, D = 0 point, and E = 0 point. Full clinical chest examination was done to find out any symptoms or signs suggestive of interstitial lung disease (ILD).

2.2. Laboratory tests

The following laboratory tests were evaluated: full blood count, erythrocyte sedimentation rate (ESR), C-reactive

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protein (CRP), and total hemolytic complement activity (CH50). Auto-antibodies were screened at the base line visit and included each of the following: antinuclear antibody (ANA), anti-Ro, anti-La, Anti-phospholipid (IgM, IgG), anti-Smith (anti-Sm), anti-ribonucleoprotein (anti-RNP), and anti-double stranded Deoxyribonucleic acid (anti-dsDNA). The ANA was measured using immunofluorescence; antibodies to dsDNA were measured by enzyme linked immunosorbent assay (ELISA) or Farr assay. Testing for extractable nuclear antigens (anti-Ro, anti-La, anti-Sm and anti-RNP) was done by ELISA followed by a confirmatory immunoblot. Seropositivity was defined as one or more positive assays for that particular antibody measured at any point during a patient's disease course. Clinical laboratory tests were performed according to standard hospital laboratory procedures.

2.3. Pulmonary function tests (PFT)

All patients enrolled in the study were subjected to pulmonary function tests within not more than 2 months from radiological evaluation. The tests included spirometry and diffusion capacity for carbon monoxide (DL_{CO}). Spirometry was performed according to the American Thoracic Society standards [13]. The DL_{CO} was determined with the single breath method according to the American Thoracic Society standards [14]. Actual results of PFT are expressed as the percentage of predicted values. DL_{CO} values were corrected for hemoglobin concentrations according to the formula proposed by Burgess et al. [15] to obtain DL_{CO} values under standard conditions.

An abnormal PFT was defined as $<80\%$ predicted forced vital capacity (FVC), $<80\%$ predicted DL_{CO}, or a Forced expiratory volume in 1 s (FEV1) divided by FVC (FEV1/FVC) ratio of $<70\%$ predicted; restrictive physiology on PFT was considered a VC of $<80\%$ predicted [13]. Measurements were obtained without bronchodilator administration with subjects tested in the sitting position.

2.4. Computerized tomography (CT) assessment

The CT scans were obtained with Philips machine one slice. Continuous scans were obtained with 1–1.5 mm collimation and were reconstructed with high spatial-frequency algorithm. They were obtained at suspended end-inspiratory effort with the patient in supine position and without intravenous material.

The features of interstitial lung disease by HRCT included septal lines, reticulations, traction bronchiectasis, cyst formation, and ground glass appearance. Patients were considered to have ILD if there were reticular and/or interstitial opacities with or without ground glass opacities and/or honeycombing on the chest CT scan after excluding alternative etiologies for the ILD [16]. Pleural involvement on chest imaging was defined as the presence of pleural effusions, pleural thickening, or pleural fibrosis on CXR or CT scan.

2.5. Statistical analysis

Data variables were encoded and entered into computer and data cleaning was performed. All data were described in the form of number, percent, mean, and standard deviation. Univariate analysis was performed to calculate the Odds ratio and confidence interval. Chi-square test was used for comparison of categorical data, while Student's-*t*-test was performed to compare quantitative data. p Value was level of significance was set at $p < 0.05$. Data entry and statistical analysis were performed using the Statistical Package for Social Science (SPSS) version 15.0 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Study population

Demographic and clinical characteristics of the patients are summarized in Table 1. The study group comprised 42 patients with a mean age of 29 ± 12.5 years that ranged from 16.5 to 45.5 years. Only one female patient was diagnosed as juvenile SLE, and her morphologic and serologic phenotypes were identical with those of the adult form, thus abolishing its effect being juvenile form of SLE. Thirty-seven patients were females and 5 were males, with 3 smokers in our cohort. Mean disease duration was 20 ± 4 (range 4–24) months. Past history of patients revealed none had chronic respiratory symptoms. At the

Table 1 Demographic and clinical characteristics of the systemic lupus erythematosus (SLE) patients.

Variable	SLE patients (n = 42)
Age	29 ± 12.5
Gender (female/male) (% female)	37/5 (88% Female)
Smoking No. (%)	3 (7.1)
Disease duration (months)	20 ± 4
Self-reported pulmonary symptoms	
Dyspnea No. (%)	8 (11.9)
Pleuritic chest pain No. (%)	14 (33.3)
BILAG global score	10 ± 3.8
Medications: No. (%)	
NSAIDs	21 (50)
Steroid (any dose)	37 (88)
Hydroxychloroquine	33 (78.5)
Immunomodulator[a]	38 (90.5)
Rituximab	2 (4.7)

BILAG, British Isles Lupus Assessment Group; NSAIDs, non-steroidal anti-inflammatory drugs.
[a] Immunomodulator, any of azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide.

Table 2 Autoantibody profile among the systemic lupus erythematosus (SLE) patients.

Autoantibody seropositivity No. (%)	SLE patients (No = 42)
ANA	41 (97.5)
Anti dsDNA	27 (64)
Anti-Ro	11 (26)
Anti-La	10 (23.8)
APL (IgM or IgG)	12 (28.5)
Anti-Sm	10 (23.8)
Anti- RNP	9 (21.5)

SLE, systemic lupus erythematosus; ANA, antinuclear antibody; dsDNA, double stranded deoxyribonucleic acid; APL, anti-phospholipid; Ig, immunoglobulin; Sm, Smith; RNP, ribonucleoprotein.

Table 3 Pulmonary involvement in SLE patients as detected by pulmonary function tests (PFTs), high resolution computerized tomography (HRCT) chest and pulmonary clinical manifestations.

Mode of detection	No. (%)
Abnormal pulmonary findings in the SLE patients (No. = 42)	
High resolution computerized tomography (HRCT)	12 (28.6)
Pulmonary function tests (PFT)	11 26.2)
With findings in HRCT	7 (16.7)
Without findings in HRCT	4 (9.5)
HRCT and PFT with clinical manifestations of ILD	4 (9.5)
Total No. of affected patients	18 (42.9)

ILD, interstitial lung disease.

time of examination, 8 patients were having dyspnea, while 14 complained of pleuritic chest pain. For disease activity in our patients, mean BILAG global score was 10 ± 3.8 (range 0–21). The medications given to the patients of the present study are also mentioned in Table 1.

3.2. Autoantibody profile among patients

Table 2 summarized the number and the percentage of autoantibody profile among our cohort of early SLE patients.

3.3. Lung involvement in patients

Out of the 42 SLE patients, 4 (9.52%) were found to have clinical symptoms and signs with abnormal PFT and HRCT related to ILD. The total number of pulmonary involvement was 18 (45%), detected by clinical manifestations of ILD, abnormal PFT and/or HRCT findings. Twelve (28.57%) patients showed abnormal findings in HRCT (mainly in lower lung lobe, including reticular and/or interstitial opacities with or without ground glass opacities and/or honeycombing). Two patients showed blunting of costo-phrenic angle (denoting pleural effusion) in CXR, without any radiological finding of ILD. Eleven patients (26.19%) showed abnormalities in their PFT. Only 2 patients (4.76%) showed obstructive ventilatory dysfunction (FEV1 68.5 ± 11.5) while a restrictive ventilatory dysfunction was present in 9 (21.42%) as the mean VC was 66 ± 12. Ten patients (23.8%) showed diffusion involvement with a mean DL_{CO} of 68.5 ± 13. Out of the 11 patients with abnormal PFT, 7 (16.66% of total number of patients) patients also had abnormal HRCT findings. Table 3 illustrates these results.

3.4. Clinical interrelationships

Tables 4 and 5 show univariate analysis of factors associated with an abnormal forced vital capacity and abnormal high resolution computerized tomography, respectively, in patients with early systemic lupus erythematosus. Demographic features, Clinical manifestations, autoantibody profile, HRCT chest abnormalities and forced vital capacity abnormalities (alternatively and respectively) and current medications were correlated with an abnormal FVC and abnormal HRCT (respectively) among the study population. Variants that were significantly associated with an abnormal FVC (< 80%) and abnormal HRCT were found to be identical with exception

Table 4 Univariate analysis of factors associated with an abnormal forced vital capacity in patients with early systemic lupus erythematosus.

Variable	Odds ratio	95% Confidence interval	*p*-Value
Clinical characteristics			
Age	2.32	0.6–10.33	0.3
Gender	0.91	0.94–1.13	0.5
Smoking	2.34	0.93–4.11	0.05
Disease duration	0.99	2.03–2.13	0.03
Self-reported pulmonary symptoms	4.23	1.36–7.67	0.001
BILAG global score	2.22	2.00–2.53	0.006
Autoantibody profile			
ANA	1.10	0.34–3.33	0.1
Anti dsDNA	2.99	0.93–9.01	0.001
Anti Ro	0.88	0.43–2.78	0.2
Anti La	0.73	0.19–3.07	0.1
APL (IgM or Ig G)	2.34	0.88–8.37	0.01
Anti Sm	3.58	2.13–11.43	0.002
Anti-RNP	4.43	1.89–12.51	0.005
HRCT chest abnormalities	1.37	1.03–2.37	0.001
Current medications			
NSAIDs	1.66	0.32–3.82	0.1
Steroid (any dose)	2.95	1.67–8.33	0.005
Hydroxychloroquine	1.66	0.32–3.82	0.3
Immunomodulator therapy	2.01	1.09–12.35	0.002
Rituximab	3.11	1.11–8.33	0.001

BILAG, British Isles Lupus Assessment Group; ANA, antinuclear antibody; dsDNA, double stranded deoxyribonucleic acid; APL, antiphospholipid; Ig, immunoglobulin; Sm, Smith; RNP, ribonucleoprotein; HRCT, high resolution computerized tomography; NSAIDs, non steroidal anti-inflammatory drugs.

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Table 5 Univariate analysis of factors associated with abnormal high resolution computerized tomography (HRCT) in patients with early systemic lupus erythematosus.

Variable	Odds ratio	95% Confidence interval	*p*-Value
Clinical characteristics			
Age	2.12	0.7–9.83	0.2
Gender	1.01	0.97–1.19	0.6
Smoking	2.54	0.95–4.18	0.05
Disease duration	0.91	2.13–2.19	0.04
Self-reported pulmonary symptoms	4.11	1.21–8.07	0.002
BILAG global score	1.99	1.80–2.59	0.005
Autoantibody profile			
ANA	1.22	0.44–3.43	0.2
Anti dsDNA	3.22	0.83–9.11	0.003
Anti Ro	0.87	0.33–2.18	0.1
Anti La	0.83	0.11–2.97	0.2
APL (IgM or Ig G)	2.31	0.99–8.77	0.05
Anti Sm	4.08	2.23–10.43	0.003
Anti-RNP	1.42	0.81–3.41	0.06
Forced vital capacity abnormalities	1.44	1.01–2.65	0.002
Current medications			
NSAIDs	1.64	0.37–3.92	0.2
Steroid (any dose)	2.85	1.77–7.93	0.003
Hydroxychloroquine	1.56	0.22–3.92	0.2
Immunomodulator therapy	2.11	1.19–12.25	0.001
Rituximab	2.89	1.21–7.33	0.001

BILAG, British Isles Lupus Assessment Group; ANA, antinuclear antibody; dsDNA, double stranded deoxyribonucleic acid; APL, anti-phospholipid; Ig, immunoglobulin; Sm, Smith; RNP, ribonucleoprotein; NSAIDs, non-steroidal anti-inflammatory drugs.

of insignificant correlation of abnormal HRCT with Anti-RNP (p 0.06). Variants that were significantly associated with an abnormal FVC (< 80%) were smoking, long disease duration, self-reported pulmonary symptoms (p 0.001), BILAG global score (p 0.006), Anti dsDNA (p 0.001), Anti-phospholipid (IgM or IgG) (p 0.01), anti Sm (p 0.002), anti-RNP (p 0.005), HRCT abnormalities (p 0.001), current medication of steroid (any dose) (p 0.005), immunomodulator therapy (p 0.002), and Rituximab therapy (p 0.001). Variants that were significantly associated with an abnormal HRCT were smoking (p 0.05), long disease duration (p 0.04), self-reported pulmonary symptoms (p 0.002), BILAG global score (p 0.005), Anti dsDNA (p 0.003), Anti-phospholipid (IgM or IgG) (p 0.05), anti Sm (p 0.003), anti-RNP (p 0.001), FVC abnormalities (p 0.002), current medication of steroid (any dose) (p 0.003), immunomodulator therapy (p 0.001), and Rituximab therapy (p 0.001).

4. Discussion

Respiratory symptoms and abnormal lung function are relatively common in SLE. There have been many studies concerning pulmonary involvement in patients with SLE. Most of these studies relied upon the characteristics of PFT and HRCT for picking up abnormal lung function in this sector of the patients [10,17,18]. Therefore; we attempted to assess the lung involvement through PFT and HRCT in early diagnosed SLE patients and correlate this involvement with clinical and immunological profile in patients. This was considered with intension for revealing how early SLE patients have their lung involved, and tried to correlate the involvement with multiple patient's variants. Pulmonary involvement in patients with SLE depending upon HRCT as well as lung physiology studies has been addressed in a wide range of reports. These reports have denoted evident proven findings; yet little have been addressed for early SLE disease [7,19,20]. Emerging data of our results emphasized that 9.5% of our early SLE patients have definitive lung involvement as detected by clinical manifestations of ILD as well as abnormalities of the PFTs and HRCT chest. A total of 42.9% of the studied patients had an element of pulmonary involvement as detected by PFT and HRCT; these patients may develop "manifest" ILD in due course of their SLE disease. Of note that, one of our patients was of juvenile SLE variety. Her morphological, serological characters were not differentiated with adult form, and her results cannot be relied upon for differentiation pulmonary involvement between adult and juvenile forms. Further longitudinal study may be required to follow up those patients to detect any clinical manifestation of conversion to clinically "manifest" ILD.

In comparison to our findings, Nakano et al. found that impairment of DL_{CO} was frequently observed in SLE patients who had no clinical respiratory abnormalities and that no significant correlation was found between impairment of DL_{CO} and disease activity of SLE. DL_{CO} was reduced in 47% of their patients and a restrictive impairment of PFT was observed in 8%. The prevalence of pulmonary fibrosis was 13% [21]. However, Silberstein et al. showed that pulmonary abnormalities do not correlate with immune parameters of their cohort [22]. Conflicting results have been published concerning the correlation among HRCT findings, pulmonary symptoms,

and physiologic studies in SLE patients. One prospective study of 34 patients with SLE found abnormalities detected by HRCT, pulmonary function studies, or chest radiography in 70, 41, and 24 percent, respectively [23]. No correlation existed among HRCT, pulmonary function studies, and pulmonary symptoms. In contrast, another prospective study of 48 patients found that abnormalities on HRCT were associated with symptom duration and pulmonary function abnormalities [24].

We have analyzed factors associated with an abnormal forced vital capacity as well as HRCT in patients with early SLE. Notably, an abnormal FVC and HRCT were detected in a sector of our cohort. In both abnormal FVC and HRCT, a significant correlation was found with smoking, disease duration, self-reported pulmonary symptoms, BILAG score, Anti dsDNA, Anti-phospholipid (IgM or Ig G), anti Sm, HRCT abnormalities, current medication of steroid (any dose), Immunomodulator therapy, and Rituximab therapy. However, anti-RNP was found to be significantly correlated with abnormal FVC but not with abnormal HRCT which may need further work for clarification and explanation. These variants can be considered as ''predictors'' for poor pulmonary involvement in SLE patients and may be related to forthcoming aggressive lung disease. There are not enough reports addressing factors associated with an abnormal forced vital capacity in patients with early SLE. Our results are in agreement with Allen et al. [9] who reported FVC < 80% among factors that were associated with increasing disease duration, the presence of dyspnea, pleuritic chest pain, a history of pleuritis, total systemic lupus activity measure score, seropositivity for anti-dsDNA, anti-Sm, anti-RNP, current use of prednisone, and current use of hydroxychloroquine and a trend toward a significant association between pleural involvement on chest imaging and an abnormal FVC. Of note that their cohort of patients is not selected as early SLE patients, yet this was found to be very close to our results and ascertained those variables as predictors for aggressive lung disease in coming future in SLE patients. Longitudinal follow up studies are needed to trace those variables in patients with early SLE during their disease course.

It can be concluded that ILD occurs as early as in the first 2 years in the course of SLE patients. There was a clear predilection of ILD with certain variables in our cohort of patients which may be considered as predictors for forthcoming aggressive lung disease which needs further work. Many articles have explored the pulmonary involvement in SLE patients by different means, yet few were found to disclose this involvement as early as the first 2 years of illness. In this view, we still miss much data to compare our findings with and need further studies with a wider sample size to confirm the present results. Furthermore, a longitudinal study is needed to verify our data regarding disease activity correlation with incidence of early pulmonary involvement in SLE disease course.

Disclosure statement

The authors disclose no conflict of interest.

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