CASE REPORT

Systemic Lupus Erythematosus and Occupational Exposure to Solvents: A Case Report

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Abstract

Introduction: Systemic Lupus Erythematosus (SLE) cases have been growing over the years, and the role of environmental agents are at the center of investigations. However, few studies have addressed the role of solvents. Therefore, we reported an SLE case in a patient with long-term low-level exposure to organic solvents in the workplace.
Case Report: A 58-year-old black female attended a teaching hospital evaluation due to oral ulcers, 14 kilos loss, and leukopenia. Her occupational history revealed a 24-year exposure to organic solvents with inadequate protection. After investigation, we made an SLE diagnosis related to solvents based on clinical presentation and laboratory tests (anemia, leukopenia, hypocomplementemia, positive antinuclear antibodies, and biomarkers of exposure). The patient's treatment included corticosteroids, immunosuppressive, and antimalarial drugs. As a result, she gradually improved in clinical and laboratory conditions.
Discussion: We addressed the potential role of solvents in developing SLE in this case report regarding a patient chronically exposed to them. SLE is a multifactorial disease triggered in genetically-prone individuals by environmental exposure. Although few studies have addressed the relationship between solvents and SLE with mixed results, strong evidence links them with other autoimmune diseases. There is biological plausibility for solvents triggering SLE, as autoimmune diseases share clinical presentation, genetic factors, and physiopathologic mechanisms.
Conclusion: Our case highlights the potential role of solvents in developing SLE. Although there are mixed results on this relationship, strong evidence associates them with other autoimmune diseases. Considering the wide use of solvents in many contexts and the similarity between autoimmune diseases, we recommend further investigations.

Keywords: Lupus Erythematosus, Systemic; Occupational Exposure; Solvents.

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a complex multisystem autoimmune disease characterized by the production of antibodies against nuclear self-antigens and deposits of the immune complex [1]. Its incidence and prevalence have been growing gradually over time, with a considerable variation between geographic regions [2]. Factors contributing to this include non-uniform SLE case definitions, differences in study design, population structure (sex and ethnicity), and environmental exposure [2]. SLE affects more women (90%) in their reproductive ages, Black, Hispanic and Asian populations, and family units with a history of SLE or related autoimmune diseases [3].

It is a multifactorial disease triggered in genetically susceptible individuals by environmental exposure [4]. It has been estimated that 56% of the SLE risk comes from environmental factors, with the weight of epidemiologic evidence varying by agent [5]. The strong and consistent positive associations point to current smoking, exogenous estrogens (oral contraceptives and postmenopausal hormone replacement therapy), and silica/silicate exposure [3,5,6]. In addition, other potential risk factors like exposure to solvents have been identified [3,8,9]. Robust evidence has been presented linking organic solvents with other autoimmune diseases, such as rheumatoid arthritis [6]. However, although there is a scarcity of literature addressing the association between solvents and SLE, occupations involving their use, and environmental exposure to trichloroethylene, which have been associated with increased SLE risk [3,8-10, 7-10]. Therefore, we aim to discuss the potential role of solvents by reporting a case of SLE with a history of chronic exposure to organic solvents in the workplace.

CASE REPORT

A 58-year-old black woman resident in the urban area of

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Rio de Janeiro, and a gun factory worker. She attended the Toxicology department of a teaching hospital with a history of persistent leukopenia (over two years), tiredness, loss of 14 kilos, and complaint of lesions in the lip and hard palate over the last two months. Physical exam revealed an emaciated patient with an erythematous area surrounded by white radiating striae of the hard palate and lips with intense desquamation, ulcers, and erythematous areas. She denied previous pathologies, alcohol consumption, smoking (current or past), regular use of medication, hormonal replacement, or autoimmune disease in her family. Also, she reported menopause at age 52 and had no history of residential and/or agriculture pesticides use or previous residence in farms or rural areas. Regarding her occupational history, she worked an 8-hour shift (48-hour week) for 24 years as a quality assurance assistant at a gun factory. She was the only employee responsible for cleaning the warlike pieces in a closed room with central air conditioning and exhaustion. Her activities involved using the following organic solvents: acetone, butanol, benzene, ethylbenzene, toluene, xylene, styrene, and trichloroethylene. The company provided the uniform, consisting of long pants, a blouse, a long-sleeved lab coat, closed shoes, and personal protective equipment, including silicone gloves, protective earplugs, and a respiratory mask. However, she reported intermittent use of the latter. The reports of her annual occupational exams, revealed leukopenia (Table 1), exposure to several solvents, and a bilateral mild sensorineural hearing loss (data not shown). The company's workplace air monitoring results were within the permitted thresholds stipulated by the Brazilian Labour Ministry (Regulatory Standard *nº 15*), which uses the Threshold Limit Values (TLVs) of the American Conference of Governmental Industrial Hygienists of 1977, adapted to Brazilian working conditions. Table 2 displays the air and biological monitoring performed.

In the last couple of years working, a transference to a bureaucratic activity occurred on medical recommendation due to the persistent leukopenia related to solvent exposure after investigation.

Table 1. Patient's hematological historical series

Year	Hematocrit (%)*	Leukogram (mm^3)**	Platelets (mm^3)***
1984[#]	42	4600	200.000
1985-2011	38-42	4100-6050	185.000-210.000
2012	40	3000	191.000
2013[##]	39-40	2900-3400	175.000-220.000
2014	30	2100	160.000

*Reference value for hematocrit: 37-47%; **Reference value for leukogram: 4000-11000 mm^3; ***Reference value for platelets: 150.000-450.000 mm^3
[#] Admission exam; [##] Transfer to bureaucratic activity

Table 2. Air monitoring at the workplace and patient's biomarkers of exposure

	Air monitoring	Maximum Concentration Observed	Brazilian Threshold Limit Value (TLV)*	European Union Limit Value for 8 hours
Solvents				
	Acetone (ppm)	610	780	500
	Ethylbenzene – EB (ppm)	31	78	100
	Styrene – ST (ppm)	40	78	20
	Toluene (ppm)	36	78	50
	Xylene (ppm)	20	78	50
	Benzene (ppm)	0.4	1.0	1.0
	Trichloroethylene (ppm)	18	78	10
	Methyl ethyl ketone (ppm)	39	155	200
	Methyl isobutyl ketone (ppm)	10	NA[#]	20
	n-Hexane	7	NA[#]	20
Metals				
	Lead (mg/m^3)	0.07	0.1	0.15
	Chromium (mg/m^3)	ND[##]	NA[#]	0.005
	Biomarkers of exposure	Maximum Concentration Observed	Brazilian Biological Exposure Indice (BEI) **	European Union Biological Limit Value (BLV)
Solvents				
	Acetone (mg/L) – urine	20.0	25.0	50.0
	Phenylglyoxinic acid (g/g Cr) + Mandelic acid (g/g Cr) – urine	0.10	0.15 (EB) 0.40 (ST)***	0.70 (EB) 0.40 (ST)***

Table 2. Continued.

Biomarkers of exposure	Maximum Concentration Observed	Brazilian Biological Exposure Indice (BEI) **	European Union Biological Limit Value (BLV)
Hippuric acid (g/g Cr) – urine	0.97	2.50	-
Methyl hippuric acid (mg/g Cr) – urine	0.03	1.50	1.00
Trans-trans-muconic acid (µg/g Cr) – urine	200	500	200
Trichloroacetic acid (mg/L) – urine	2.50	15.0	15.0
Methyl ethyl ketone (mg/L) – urine	ND[##]	2.00	2.00
Methyl isobutyl ketone (mg/L) – urine	0.50	1.00	1.00
2,5 Hexanedione (mg/L) – urine	0.16	0.40	0.20
Metals			
Lead (µg/100ml) – blood	15.0	60.0	70.0
Chromium (µg/L) – urine	4.00	25.0	25.0

* According to the Brazilian Labour Ministry (Regulatory Standard nº15), for 48 hours/week of work
** According to the Brazilian Labour Ministry (Regulatory Standard nº7)
*** EB – ethylbenzene and ST – styrene
[#]NA – data not available
[##]ND – not detected

Routine hematological evaluations were indicative of normochromic normocytic anemia, leukopenia with lymphopenia, and high levels of reactive C protein. In addition, biopsy and histopathological examination of the lower lip and hard palate displayed degeneration of the basal layer with subepithelial inflammatory infiltrate. Further investigation revealed a reduction in the complement system C3 and C4 components, positive ANA, anti-dsDNA, and anti-SSA, and elevated erythrocyte sedimentation rate, which corroborated the criteria for SLE diagnosis (Table 3). Therefore, the Rheumatology department started a follow-up and managed her with immunosuppressive drugs, antimalarial, and corticosteroids. She evolved with a gradual improvement of clinical and laboratory conditions and subsequent stabilization.

Table 3. Patient's laboratory tests for diagnostic evaluation

	Concentration	Reference value
Complete blood count		
Red Cells (millions/mm³)	3.69	4.20-5.40
Hemoglobin (g/dL)	10.1	12-16
Hematocrit (%)	30	37-47
Mean Corpuscular Volume (fl)	87.1	81-95
Mean Corpuscular Hemoglobin (pg)	30	27-31
RDW (%)	16.4	11.5-14.8
Leukocytes (mm³)	2100	4000-11000
Basophils (mm³)	0	0-100
Eosinophils (mm³)	21	100-300
Metamyelocytes (mm³)	0	1-1
Myelocytes (mm³)	0	0-0

Table 3. Continued.

	Concentration	Reference value
Cone or rod cells (mm³)	0	200-500
Segmented neutrophils (mm³)	1365	2300-5900
Lymphocytes (mm³)	441	1500-3900
Monocytes (mm³)	273	200-500
Platelets (mm³)	160.000	150.000-450.000
Iron kinetics		
Iron (mcg/dL)	61	60-180
Total iron binding capacity (mcg/dL)	124	250-450
Ferritin (ng/dL)	1931	5-148
Transferrin (mg/dL)	105	200-360
Transferrin saturation (%)	49	20-50
Inflammation		
C3 (mg/dL)	65	90-180
C4 (mg/dL)	2	10-40
C-reactive protein (mg/dL)	7.1	0-5
Erythrocyte sedimentation rate (mm/h)	140	15
Antibodies		
Antinuclear antibodies (ANA)	> 1/1280	1/128
Anti-dsDNA	1/160	1/10
Anti-SSA	75	< 7
Antiglobulin test	Negative	Negative
Others		
IgM EBV*	NR**	NR**
IgG EBV	NR**	NR**
25OH Vitamin D (ng/ml)	30	20-100

* EBV: Epstein Barr Virus; ** NR: non-reactive

DISCUSSION

Lupus is a multifactorial disease stemming from interactions between genetic and environmental factors that lead to a variation in disease expression [4,10]. Herein, we reported a case of SLE in a middle-aged black woman with a history of long-term low-level exposure to a mixture of organic solvents in the workplace.

Our patient had the characteristic sociodemographic profile of SLE cases, as at least 90% encompass women even at an older age with a female-to-male ratio of 8:1 and African-American females are > 2.5 times more affected than white females [5,11]. Also, it occurred in an urban area, where this disease is more prevalent compared to rural area [11]. However, extensive research fails to explain the large phenotypical diversity, age of onset, and ethnic and sex differences [3,5,10]. Hence, the role of environmental agents has gained much attention in order to understand these phenotypic differences in autoimmune diseases [6,10,12]. Several studies have addressed its association with SLE, and the most robust evidence pointed to current smoking, exogenous estrogen, and crystalline silica/silicate exposure [3,5,6]. In addition, other risk factors such as air pollution, infections (e.g., Epstein Bar), ultraviolet light, vaccinations, and other chemicals (mercury, pesticides, and solvents), also should deserve further consideration due to preliminary human findings and experimental animal research, as well as biological plausibility related to oxidative stress induction [3,10,13].

We hypothesized the potential role of solvents in developing SLE in our patient, first based on her long-term low-level exposure corroborated by the documentation of occupational air and biological monitoring and aggravated by the inadequate use of the respiratory mask. Although the levels of the biomarkers observed were lower than the biological exposure index, they do not exclude a possible role of occupational exposure in health impairment [14]. Furthermore, although the low-level effects do not indicate toxicity, they could represent subtle effects more consistent with the disease development in long-term exposures [15]. Last but not least, evidence suggests that chronic exposure to some environmental agents needs to be present before the onset of SLE [16]. It is also important to point out that we ruled out other risk factors such as exogenous estrogen, current smoking, silica/silicate or mercury exposure, EBV infection, pesticide use for bug control, gardening or other agricultural activities, and regular medication consumption [3].

On the other hand, the relevant literature points to an increased risk for SLE in occupations and activities involving solvents use [8,9,17,18], acceleration of lupus development, and induction of an autoimmune response (autoantibody expression) in lupus-prone mouse models and humans [18-22 7,19-22]. Furthermore, one of the solvents to which she was exposed, trichloroethylene, has been implicated as a risk factor for developing lupus and is one of the most widely studied [3,7,19-23]. Finally, there are robust data linking solvents to other autoimmune diseases, such as systemic sclerosis, rheumatoid arthritis, multiple sclerosis, and primary vasculitis [6,12,24,25]. These diseases share clinical presentation, physiopathological mechanisms, and genetic factors, indicating that they have common origin, known as autoimmune tautology [24]. This latter assumption is essential because very few studies have investigated the association between solvents and SLE, showing mixed results [7-9,13,17-23,26-29]. The explanations for these discrepancies may encompass differences in study design, its methodologies, such as sample size, population characteristics (age, ethnicity, sex), exposure assessment, and control of bias. Therefore, despite the inconsistent results, further investigation on the role of solvents in developing SLE is advisable as they are a class of chemicals widely used in residential and occupational contexts, and there is convincing data on their role in other autoimmune diseases [3,13].

This study has some limitations, starting with its design that precludes causal-effect assumption. Secondly, we had no data about other workers' health status. Thirdly, we should shed some light on the constraints of air and biological monitoring of chemicals made annually on a single measurement, as they may not represent the dynamic in levels of exposure. This issue is significant for substances with quick metabolization, such as solvents, because their biomonitoring does not reflect total exposure over time [30]. Also, we addressed a group of organic solvents and could not specify which one could be responsible. Furthermore, it is worth noting that considerable variability exists within and between-person in biomarker levels affecting the precise characterization of the exposure-disease relationship [31]. Last but not least, exposure to other agents, such as heavy metals, is common in gun factories. Both organic solvents and heavy metals have been linked to many toxic effects through inflammation, mitochondrial dysfunction, oxidative stress, and oxidative DNA damage [32]. However, neither chromium nor lead, solely, has been related to SLE [3,4]. Besides, the investigation of chemical mixtures in SLE has not been addressed. Finally, we cannot dismiss that our patient had the characteristic socio-demographic profile of most SLE cases, represented by black females living in urban areas [11].

CONCLUSION

Our case highlights the potential role of solvents in developing SLE. The patient had long-term low-level exposure to this class of chemicals, and chronic exposure seems necessary before the onset of SLE. Although this topic has mixed results, strong evidence links solvents with other autoimmune diseases. Considering the wide use of solvents in many contexts and the similarity between autoimmune diseases, it seems justifiable to carry out further investigations.

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