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Discoid lupus in antiphospholipid syndrome: case description and literature review

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Abstract. – OBJECTIVE: The aim of the study was to report about a patient with discoid lupus erythematosus (DLE) who developed antiphospholipid syndrome (APS) 12 years after DLE diagnosis and review related literature.

PATIENTS AND METHODS: This is a case report of a 34-year-old woman with DLE who developed APS. A review of articles published in the PubMed/MEDLINE, LILACS, and SciELO databases from 1966 to October 2020 was conducted using the following search terms: "antiphospholipid syndrome," "antiphospholipid antibodies," and "discoid lupus erythematosus". No language limitation was applied.

RESULTS: Besides the present case, 5 case reports were identified. One case-control and two cross-sectional studies on antiphospholipid antibodies with or without APS in DLE were also reviewed. These studies revealed that APS can develop even 37 years after DLE was diagnosed. The case-control study found that patients with DLE have more anticardiolipin antibodies than controls. In contrast, one cross-sectional study showed a low prevalence of antiphospholipid antibodies in their group of patients, which was similar to findings in the general population.

CONCLUSIONS: This study reviewed previous articles on DLE cases associated with antiphospholipid antibodies and/or APS, adding a new case description.

Key Words:
Discoid lupus, Systemic lupus erythematosus, Antiphospholipid syndrome, Hughes syndrome, Thrombophilia, Autoimmunity, Autoantibodies.

Introduction

Antiphospholipid syndrome (APS) is associated with recurrent pregnancy morbidity during pregnancy and/or thrombotic events[1]. Primary APS (pAPS) refers to APS that may appear isolated. Secondary APS may be associated with other autoimmune conditions, a common example being systemic lupus erythematosus (SLE)[1]. APS has also been associated with Sjögren's syndrome, rheumatoid arthritis, systemic sclerosis, systemic vasculitis, and dermatomyositis[2].

To fulfill the diagnostic criteria, antiphospholipid antibodies (APLAs), such as lupus anticoagulant (LA), anticardiolipin antibodies (aCLs), and/or anti-β2-glycoprotein I antibodies, must be persistently present[3]. Isolated APLAs may be detected in those without APS in daily practice; these autoantibodies may be found in healthy individuals, mainly in older people, or may be associated with the use of certain drugs, malignancies, and/or chronic infections[3].

DLE is the most common lesion of chronic cutaneous lupus that occurs more frequently in women in their fourth and fifth decades of life. It is a photosensitive dermatosis that may lead to the formation of disfiguring scars[4]. In almost 10% of analyzed cases, this skin alteration might also meet the SLE criteria[4]. Although APS has been commonly associated with SLE, APLAs or APS in DLE without systemic manifestations have been poorly studied thus far.

Therefore, this study reports about a patient with DLE and APS and reviews related literature.

Methods

The publication of the case description has been authorized by the patient and the Federal University of Bahia Ethical Committee.

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A search of articles published in the PubMed/MEDLINE, LILACS, and SciELO databases between 1966 and October 2020 was performed. All researched articles were based on "antiphospholipid syndrome," "antiphospholipid antibody," and "discoid lupus erythematosus." No language limitation was applied. The following parameters were used to screen published articles on the association of APS with DLE: study design, epidemiological data, and clinical features (clinical presentation of APS, detection of APS-related antibodies, interval time between diagnoses of both diseases, and sequence of disease appearance).

Two authors independently reviewed the articles and the references mentioned in each article to identify any other articles that met the inclusion criteria. Duplicate articles and studies that were insufficiently detailed or not sufficiently informative were excluded.

Case Report

A 34-year-old woman had a medical history of allergic rhinitis and a family history (cousin) of rheumatoid arthritis. She had a routine outpatient consultation in the dermatology department of a private hospital in 2003 owing to a single skin lesion on the left nasal region. Physical examination only showed an erythematous and desquamative plaque measuring approximately 1.5 cm in size with an atrophic whitish center compatible with discoid lupus (Figure 1). Her blood laboratory test results were completely normal; she was negative for antinuclear antibodies (ANAs). Her skin biopsy results were compatible with discoid lupus, as the epidermis revealed hyperkeratosis, parakeratosis, vacuolar degeneration of the basal layer, dyskeratosis, and atrophic areas with mononuclear infiltrates mainly in the perivascular and perianexial dermis. She was treated with sunscreens, 15 mg/day of prednisone, and 400 mg/day of hydroxychloroquine for 2 years, and she experienced improvement via the progressive healing of the lesion. However, in 2015, she developed a deep venous thrombosis of her left leg with popliteal vein occlusion, which was confirmed via Doppler ultrasound. She was treated with enoxaparin (60 mg, subcutaneously, twice a day) and warfarin (with a target international normalized ratio of 2-3) for 3 months. Three years later, a new thrombosis was observed in the same region; she received heparin followed by rivaroxaban and was referred to our clinic. Her lower limbs were normal; no edema was observed. Laboratory test results revealed normal blood counts and urinary sediment. ANAs, anti-centromeres, anti-Ro/SS-A, anti-dsDNA, anti-Sm, anti-Scl70, and antineutrophil cytoplasmic antibodies were all absent, and complement levels were within normal ranges. LA, immunoglobulin (Ig)G (68 GPL/mL) and IgM 16 (MPLmL) aCL were present. Screening for thrombophilia, including mutant prothrombin, factor V Leiden, protein C and S, and antithrombin III, showed negative results. Serology for infectious diseases, such as syphilis, hepatitis B and C, mononucleosis, rubella, toxoplasmosis, human immunodeficiency viruses (HIVs) 1 and 2, and human T-lymphotropic viruses I and II, were negative. After 12 weeks, the patient was still positive for LA and anticardiolipin. A diagnosis of APS was made. Rivaroxaban was switched to warfarin; 400 mg/day of hydroxychloroquine and sunscreens were continued. Her skin lesion improved, and no new thrombotic events developed. Currently, she is asymptomatic, and the skin lesion is in remission.

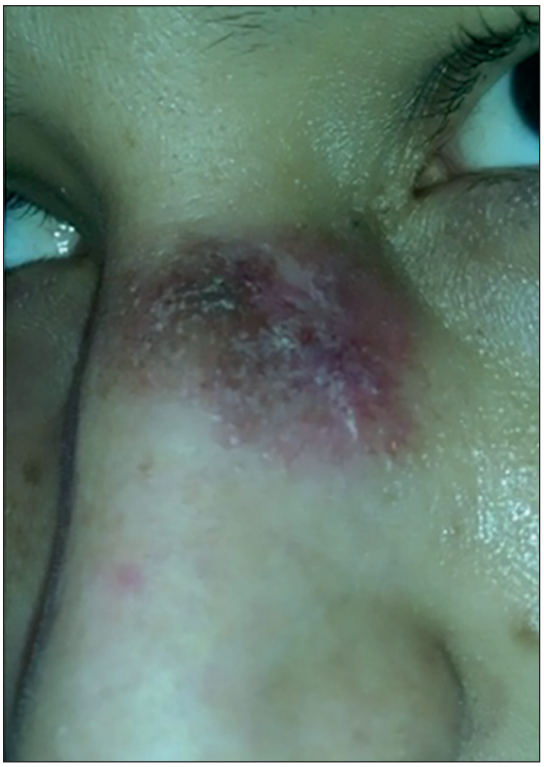

Figure 1. Discoid rash on the left nasal region.

Literature Review Results

The literature search initially yielded 23 articles; after reading the abstract, 18 articles were

Table I. Case description for the association of antiphospholipid antibody syndrome (APS) with discoid lupus erythematosus (DLE).

Author, year	Age (years), sex	Appearance order	Time between diseases	APS clinic	Observation	Positive APLAs
Fernando et al[5], 2008	64, male	DLE → APS	37 years	Stroke	SLE appeared 47 years after DLE.	aCLs, LA
Tektonidou et al[6], 2003	27, male	DLE → APS	5 years	DVT with PTE	APS appeared 3 months after thalidomide use	aCL IgG
Yilmaz et al[27], 200	45, female	N/A	N/A	Abortions, DVT	Patient with pulmonary microlithiasis. H. Zoster infection.	aCl IgG, aCl IgM
Berth-Jones[8], 1989	29, male	DLE → APS	11	Recurrent DVT	–	LA, aCl IgG
Satta et al[9], 2016	35, female	APS → DLE	1 year	PTE	–	aCl IgG, anti-beta2 glycoprotein

N/A=not available; APS=antiphospholipid antibody syndrome; APLAs=antiphospholipid antibodies; DLE=discoid lupus erythematosus, PTE=pulmonary thromboembolism, DVT=deep vein thrombosis, aCl=anticardiolipin; SLE=systemic lupus erythematosus.

excluded. Thus, eight articles were identified and included in the present study: five case reports, two cross-sectional studies, and one case-control study. The last three articles aimed to detect APLAs in patients with DLE regardless of the presence of APS. Table I contains a summary of the case descriptions. Table II has the primary data regarding the studies that aimed to detect APLAs in patients with DLE with and without APS.

Discussion

To date, the association of DLE with APS and/or the presence of APLAs has been poorly studied. In the analyzed studies, DLE preceded the occurrence of APS in most of the cases as in the presently described patient. Based on the analyzed studies, the second disease can appear or develop even 37 years after the first disease

Table II. Studies on antiphospholipid antibodies (APLAs) in discoid lupus erythematosus (DLE).

Autor, year	Study design	N	Sex	Age	Antibodies	Results	APS n/clinic	Obs
Ruffatti et al[10], 1996	Case-control	28 DLE 60 controls	19 F, 9 M	mean 44.2	aCl IgG e IgM ELISA	67.8% DLE + aCL IgG; 50% DLE + aCL IgM.	1 DLE patient with DVT and PTE	$p < 0.0001$ with controls fot both antibodies
Garcia Martin et al[3], 2013	Cross-sectional	164 with CLE	N/A	Mean 45.5	LA, aCls IgG aCl, IgM, Beta 2; + twice	3.6% +	1 with 1 abortion	Considered equal to the normal population
Mayou et al[11], 1988	Cross-sectional	52	37 F, 15 M	Range 24-78	aCl - ELISA	7+ for IgM 3+ for IgG (low titers)	None	aCl more common in patients with + ANA

N/A=not available; APS=antiphospholipid antibody syndrome, DLE=discoid lupus erythematosus, F=female, M=male; Obs=observation, PTE=pulmonary thromboembolism, DVT=deep vein thrombosis, aCl=anticardiolipin; ANA=antinuclear antibodies, CLE=cutaneous lupus (chronic and subacute lesions).

was diagnosed[5]. In one case, the clinical aspects of APS appeared soon after thalidomide use for DLE treatment, and it was questioned if this drug exposure could have worked as a "second hit" in APS[6]. An increased risk for thrombosis (22%–28%) has also been reported in patients with malignant diseases that were treated with thalidomide[6].

DLE manifests in 15%–20% of SLE cases and may precede the appearance of the systemic disease in 5%–10% of these cases[12]. This systematization more frequently occurs in patients with generalized skin disease, which is when the area under the neck is affected[13]. This systematization may occur several years after the advent of DLE, as seen in the case described by Fernando et al[5], in which SLE appeared 47 years after DLE diagnosis. Thus, it can be hypothesized that some patients from the analyzed case reports later evolved to SLE. In such a situation, one assumes that the APS is associated with SLE rather than with DLE. Approximately 40% of SLE cases may be positive for APLAs, but thrombotic events are not as expected, and their frequency is associated with the duration of SLE[14].

In the studies that described the detection of APLAs in DLE cases, the results are conflicting. While some authors found that this association more frequently occurred in DLE patients than in controls[10], others found an identical or similar prevalence in the general population[3]. In one study, these autoantibodies were tested twice[3], as required for APS classification according to the Sidney criteria[15]; in this work, the positivity rate was relatively low (3.6%), and only one patient had one abortion; no vascular events were noted[3]. The prevalence of APLAs in the general population is approximately 1%–5%, with the rate being higher in older individuals[16]. In the studies by Rufatti et al[10] and Mayou et al[11], the autoantibodies tested were only cardiolipins, which were tested for only once. Thus, the positive results may be due to intercurrent factors, such as drug use or infections. The occurrence of transient positivity for autoantibodies without APS, usually at low titers (<40 Units/mL), is not rare in infections and the use of certain drugs[17,18], which are situations frequently overlooked. Several viral infections, including hepatitis C virus, HIV, cytomegalovirus, varicella-zoster, Epstein-Barr virus, adenovirus, and parvovirus B, may be associated with the appearance of APLAs[17]. Drugs associated with the induction of APLAs, such as antiarrhythmics, anticonvulsants, antipsychotics, antihypertensives, antibiotics, and biologicals, including anti-TNF-alpha, also cause SLE or lupus-like illnesses[18]. In the case of drug-induced APLAs, they are mainly of the IgM subtype[18].

Mayou et al[11] reported that the aCL had lower titers and that those with ANA had a greater chance of being aCL positive, which raises the possibility that such patients may develop SLE in the future. Patients with APS and positive ANA are at risk for developing SLE[19].

Conclusions

The association of cutaneous DLE with APS is uncommon. The search for APLAs in DLE showed controversial findings. Future studies with a systematic dermatological evaluation of APS cohorts and the search of APLs in DLE patients are required to determine the true prevalence of this association.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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