v. 4, n. 48, 2024

International Journal of Health Science

SYSTEMIC LUPUS ERYTHEMATOSUS AND PORPHYRIA CUTANEA TARDA: A CASE REPORT

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Abstract: Introduction: as this is an infrequent association, the present study intends to report a case of a patient diagnosed with systemic lupus erythematosus associated with porphyria cutanea tarda and its clinical implications. Clinical case: patient referred to a rheumatologist due to high ANA titers presented clinical signs of hypertrichosis, acne, skin scars and blisters. Discussion and review of the literature: both pathologies can manifest themselves through blisters and photosensitivity, requiring diagnostic confirmation through laboratory tests and joint management for their treatment. Final considerations: even though the association between pathologies is rare, it is extremely important to know their clinical association and joint management, avoiding complications such as hepatotoxicity.
Keywords: Systemic lupus erythematosus, late Cutaneous Porphyria, drug-Induced Hepatitis.

INTRODUCTION

The association between Systemic Lupus Erythematosus (SLE) and Porphyria Cutanea Tarda (PCT) is rare and difficult to differentiate diagnostically (FRITSCH et al., 2012). SLE is an inflammatory autoimmune disease with abnormalities in autoantibodies, such as antinuclear antibodies (ANA), which commonly has varied cutaneous manifestations and a broad clinical and laboratory presentation (BORBA et al., 2008). PCT, the most common form of porphyrias, is a bullous disease caused by an enzymatic dysfunction, requiring laboratory confirmation through the measurement of porphyrins for its diagnosis (HERMOSILLA; TORO; MOLGÓ, 2018; VIEIRA; MARTINS, 2003). Both pathologies can manifest themselves through blisters, although this is less common in SLE, and photosensitivity (FRITSCH et al., 2012).

OBJECTIVES

The present study aims to report the association between PCT and SLE, reinforcing the clinical characteristics of the pathologies when isolated or associated, and their treatment, through a case report and a literature review. This case report will add value to the scientific community, since the mechanisms of the association are little known and the risk of complications from its treatment.

CLINICAL CASE

Female patient, 21 years old, student, sought rheumatological care in August 2021, when she was referred due to high ANA titers (1:640 - homogeneous nuclear). About 3 months ago, the patient complained of darkening of the skin, hypertrichosis (arms, hands and face), hirsutism, acne, deep scars on the back of the hands and arms, presence of blisters on the back of the hands, and photosensitivity.

She denied oral, genital, respiratory, intestinal symptoms, xerostomia, fever, xerophthalmia, lymph node enlargement or weight loss. She had no personal or family history of known chronic diseases.

Due to the presence of skin lesions, elevated ANA and photosensitivity, the diagnosis of SLE was suspected. Complementary tests were requested to aid diagnosis, and thrombocytopenia and the presence of anti-SM and anti-RNP were evident, closing the diagnosis of SLE. Furthermore, the bullous skin lesions, scars, hypertrichosis, and photosensitivity were suggestive of porphyria cutis. Therefore, an exam was requested to evaluate urinary porphyrin, which also corroborated the hypothesis of PCT.

For the treatment of SLE AND PCT, prednisone 1 mg/kg was initially prescribed with progressive reduction and hydroxychloroquine 200 mg per day, which led to remission of the hematological and cutaneous symptoms associated with SLE. However, the patient developed drug-induced hepatitis (TGO and TGP levels greater than 1000 U/l) due to hydroxychloroquine and the medication was suspended after 3 days of treatment.

Due to the hepatotoxicity associated with hydroxychloroquine, phlebotomy (3 sessions) was chosen to treat PCT, with a good response and improvement in the injuries associated with this comorbidity. Due to the difficulty in reducing corticosteroids and changes in liver enzymes, Belimumab 10 mg/kg was chosen to control SLE as a corticosteroid-sparing method. The patient presented remission of the condition and currently has SLE in remission and corticosteroids suspended.

DISCUSSION AND LITERATURE REVIEW

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a rare, chronic, inflammatory and multisystemic autoimmune disease, and is related to genetic predisposition and environmental factors, with periods of exacerbation and remission. It is a disease that occurs in all races and countries, being more common in women in the reproductive phase (BORBA et al., 2008).

According to the 2019 European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) clinical diagnostic criteria, mucocutaneous presentations can manifest as non-scarring alopecia, oral ulcers, subacute cutaneous or discoid lupus and acute cutaneous lupus. It is worth highlighting that the main clinical manifestation of SLE is cutaneous lupus (RIBEIRO et al., 2008). In addition to these criteria, the presence of constitutional (fever), hematological (leukopenia, thrombocytopenia, autoimmune hemolysis),

neuropsychiatric (delirium, psychosis, depression), serous (pleural or pericardial effusion, acute pericarditis), musculoskeletal (joint involvement) and renal (proteinuria > 0.5 g in 24 hours, lupus nephritis), are also important for defining the disease (ARINGER et al., 2019).

Among the most prevalent lesions of acute cutaneous lupus erythematosus are malar rash, maculopapular erythema, photosensitivity, alopecia, oral aphthae and vascular lesions. In the subacute form, related to anti-SSA antibodies, there are annular and psoriasiform lesions, which clinically manifest as non-infiltrating scaly plaques that mainly affect exposed parts of the trunk and upper extremities. In its chronic presentation, atrophy of the dermis and involvement of appendages are frequent, discoid lesions configure its most classic form, featuring plaques that evolve from hyperpigmentation to deep scars (RIBEIRO et al., 2008).

Treatment recommendations for cutaneous involvement of SLE are based on photoprotection, therapy with topical corticosteroids, corticosteroids and immunosuppressants. These act on acute skin lesions that respond adequately to the treatment of other clinical signs and symptoms; antimalarials are commonly used. These are indicated for localized skin lesions, whether in fluoridated or non-fluorinated form depending on the location and presentation of the lesion. These are essential to protect against photosensitivity in patients with SLE, with ultraviolet B radiation being its main cause (Brazilian Society of Rheumatology, 2006). Furthermore, smoking affects the effectiveness of chloroquine and, although eating habits are not directly related to SLE activity, in complicated cases, dietary restriction is recommended (RIBEIRO et al., 2008).

CUTANEOUS PORPHYRIA TARDA

PCT is a bullous disease caused by a dysfunction in the enzymatic activity of uroporphyrinogen decarboxylase (Urod) in the liver, acting in the biosynthesis of the heme group of hemoglobin. In addition to being the main porphyria, it generally starts in individuals over 40 years of age and is more common in women (VIEIRA; MARTINS, 2003).

PCT can be presented in 3 ways. Type 1 is the most common and corresponds to the acquired or sporadic form, associated with precipitating factors (such as viral infections or exogenous substances) that generate an enzymatic deficit, restricted to the liver. Type 2 (hereditary) results from an autosomal dominant alteration, which reduces the enzymatic activity of Urod - thus, porphyrins accumulate in the liver and are transported to the skin (in non-photoactivated form) when Urod activity is reduced. less than 20%, generating late symptoms. And type 3, which manifests itself in individuals who have normal Urod activity, but still clinically manifest PCT (HERMOSILLA; TORO; MOLGÓ, 2018).

The main risk factors for PCT are alcohol (hepatotoxic effect, induces hepatic ALA synthetase, decreases erythrocyte Urod activity), estrogens (main risk factor in women), halogenated hydrocarbons (pesticides), iron (PCT is an iron disorder dependent) and HIV. Furthermore, another risk factor is infection with the hepatitis C virus, which generates inflammation and liver necrosis and ends up increasing tissue iron or altering its normal compartmentalization in the cell; It is also noteworthy that excess iron has a synergistic effect on the pathogenicity of this virus (IRIBAS et al., 2008).

Clinical signs of PCT, although insufficient for diagnosis, generally appear on the back of the hands, forearm, face, feet and legs, through vesicles, scars with milium,

blisters (tense, generally with clear content), erosions, crusts, sclerodermiform plaques, areas of hyperpigmentation, hypertrichosis (more common in the form of lanugo, it is common to be the first clinical presentation in women), cicatricial alopecia, premature aging with solar elastosis and comedones. Less common manifestations include nausea, anorexia, diarrhea or constipation, peripheral neuropathy, insomnia, epiphora and palmar fibromatosis (HERMOSILLA; TORO; MOLGÓ, 2018; VIEIRA; MARTINS, 2003).

It must be considered that most skin lesions are characterized by photosensitivity and fragility (especially when trauma occurs), although sclerodermiform plaques can appear in places protected from sun exposure, and generally develop in more advanced stages of the disease. For better diagnostic elucidation, blood, urinary and fecal porphyria measurements are necessary (HERMOSILLA; TORO; MOLGÓ, 2018; VIEIRA; MARTINS, 2003).

Treatment for porphyrias consists of periodic phlebotomies (to reduce iron) and the use of antimalarials in cases where these are contraindicated (HERMOSILLA; TORO; MOLGÓ, 2018). The use of hydroxychloroquine in low doses can be an alternative for managing the disease, but stopping risk factors (such as smoking, estrogen exposure and alcoholism) must be done together, in addition to reducing iron levels in the blood. Patients with hereditary hemochromatosis have a greater chance of recurrence when treated exclusively with hydroxychloroquine (RUDNICK; BONKOVSKY, 2009).

ASSOCIATIONS BETWEEN PATHOLOGIES

The cutaneous manifestations of SLE have a wide clinical variety, however, bullous manifestations are rare and difficult to diagnose. For this reason, it is important to differentiate between dermatitis herpetiformis, pemphigus, pharmacodermias, epidermolysis bullosa acquisita, and, although rare (less than 5% of cases), PCT (FRITSCH et al., 2012).

The possible causes of the association between PCT and SLE are poorly known. Even so, it is known that the relationship between these pathologies may be related: because they have a predisposing genetic component on the same chromosome; porphyria generates an immunological response conducive to lupus through cellular damage; by the accumulation of porphyrins, it activates the complement system and increases neutrophil chemotaxis in the presence of ultraviolet rays; and because porphyria autoantigens facilitate the formation of autoantibodies (HAENDCHEN et al., 2011).

Regarding treatment regimens, the coexistence of SLE and PCT can cause difficulties. Antimalarials (such as Hydroxychloroquine and Chloroquine), common to treat SLE, can often be contraindicated or indicated in reduced doses, as they increase the risk of dose-dependent porphyrinuria, generating fever, nausea, hepatocellular damage and liver necrosis. As a result, in cases where PCT and SLE are linked, low-dose antimalarials (half the typical amount, just twice a week) are indicated (FRITSCH et al., 2012).

Sun exposure must be considered for both diseases, which can be exacerbated by sun exposure (FRANK; GUTIÉRREZ, 2010). Therefore, at the time of diagnosis, one must remember the symptoms associated with SLE and PCT, which include photosensitivity and bullous lesions (FRITSCH et al., 2012).

Uroporphyrin is responsible for the skin photochemical reaction when photoexposure occurs. Furthermore, most sunscreens do not provide effective protection, except those that contain titanium dioxide and zinc oxide in their dermocosmetic composition (FRANK; GUTIÉRREZ, 2010).

Knowing the effects of antimalarials on PCT (hepatotoxicity and maintenance of existing disease) and cutaneous lupus erythematosus (excellent response to treatment, even at low doses), an option for these concomitant diseases is phlebotomy (300 ml of blood weekly), which is not recommended for patients with anemia, and the use of antimalarials in reduced doses (FRANK; GUTIÉRREZ, 2010; GIBSON; MCEVOY, 1998; VAN TUYLL VAN SEROOSKERKEN, 2007). With the use of 125 mg of chloroquine 3 times a week, remission is expected in up to 9 months; For the disease to remit more quickly, the best therapy is to combine these approaches (FRANK; GUTIÉRREZ, 2010).

Antimalarial therapy emphasizes the importance of recognizing coexisting SLE and PCT, especially since there is a need to avoid high doses of these medications. A dosage of 500 to 1000 mg of Chloroquine increases the risk of acute hepatotoxic reaction and increases uroporphyrin levels in the urine. Estrogen and oral contraceptives must be used with caution in patients with both diseases (GIBSON; MCEVOY, 1998).

It is suggested that in the processes that cause hepatotoxicity, constitutional symptoms and subsequent long remission process are caused by the selective death of mitochondria, which are largely responsible for the overproduction of porphyrins. Fever, lethargy, abdominal pain and drastically elevated aminotransferase levels are common symptoms of the reaction that occurs after administration of high dose chloroquine in a patient with PCT (LIU, 1995).

Low doses of chloroquine (125 or 250 mg, twice a week) were associated with greater therapeutic success, as they do not worsen liver damage or cause retinopathy. The administration of chloroquine is followed by an increase in porphyrin secretion in the urine and a slight increase in liver transaminases at the beginning of treatment, which must not be discontinued until biochemical remission (uroporphyrin < 100μg/24h). Despite being effective, recurrence occurs earlier than in relation to phlebotomy. Hypotheses for the drug's mechanism of action include the formation of a complex with uroporphyrin, which is excreted by the liver into bile, and an increase in the excretion of porphyrins by exocytosis, with a porphyrinostatic effect, inhibiting the formation of porphyrins. (VIEIRA; MARTINS, 2003).

FINAL CONSIDERATIONS

Considering the rare association between SLE and PCT, the complexity of such pathologies and their clinical differentiations, it is essential that a compatible clinical picture raises suspicion of the injuries. Joint treatment is based on the use of low-dose antimalarials to treat SLE, phlebotomies to reduce the iron concentration caused by PCT, and photoprotection, as both injuries can be exacerbated by sun exposure. However, the use of hydroxychloroquine or chloroquine in high doses has a hepatotoxic effect and generates overproduction of porphyrins, which can result in drug-induced hepatitis and even liver necrosis.

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