Increased photosensitivity? Case report of porphyria cutanea tarda associated with systemic lupus erythematosus

Scheila Fritsch[1], Adma Silva de Lima Wojcik[2], Lilian Schade[1],
Milton Marcio Machota Junior[3], Fabiane Mulinari Brenner[4], Eduardo dos Santos Paiva[5]

ABSTRACT

The association of porphyria cutanea tarda (PCT) and systemic lupus erythematosus (SLE) is rare. Systemic lupus erythematosus, of complex pathophysiology and pleomorphic clinical manifestations, is similar to PCT regarding photosensitivity. One finding that can differentiate both diseases is the presence of cutaneous blisters, which are rare in SLE, but characteristic of PCT. We report one case of the association of PCT and SLE and revise the literature, emphasizing pathophysiological, clinical and therapeutic aspects. One relevant information for clinical practice relates to the treatment of SLE with antimalarials, which is a risk for PCT.

Keywords: systemic lupus erythematosus, porphyria cutanea tarda, porphyrias.

INTRODUCTION

Porphyrias are metabolic disorders caused by enzymatic abnormalities in the heme biosynthesis pathway, a substance required for the synthesis of hemoglobin and cytochromes.[1] Depending on the mutation responsible for the enzymatic abnormality, different metabolites accumulate. Eight types of porphyria are known.[1] They are classified as hepatic or cutaneous (depending on where the major amount of precursors accumulate), or as acute, rare recessive or cutaneous porphyrias. The last group comprises porphyria cutanea tarda (PCT), a highly photosensitive bullous disease. Its association with systemic lupus erythematosus (SLE) has already been reported, and despite the lack of data about the prognosis of that association, it can have therapeutic implications. Thus, we report a case of the association of SLE and PCT, and review the literature about the topic.

CASE REPORT

The patient is a 50-year-old doorman, previously healthy, on no medication and with no significant family history. He reported cutaneous hyperpigmentation of sun-exposed areas for four years. He also reported the formation of blisters on the skin of the upper limbs and face one year before; after rupturing, they originated ulcerated crusted lesions that healed with hyperpigmentation and milia formation (Figure 1). Urine porphyrinogen excretion was 3 mg/24h (reference < 1.5 mg), and the biopsy of a vesicular lesion on the dorsum of his hand was compatible with porphyria (Figure 2). After phlebotomies, the lesions healed. Six months later, the patient had arterial hypertension, low platelet count (76,000 platelets) and nephrotic proteinuria (8.25 g/24h). He tested positive for hepatitis C (HCV) and negative for HCV-RNA. His transaminases were within the normal range, and his abdominal ultrasound showed no

Received on 04/22/2011. Approved on 09/05/2012. The authors declare no conflict of interest.
Universidade Federal do Paraná – UFPR.
1. Resident Physician in Internal Medicine, Hospital de Clínicas, Universidade Federal do Paraná – HC-UFPR
2. Dermatologist, HC-UFPR
3. Resident Physician in Anatomical Pathology, HC-UFPR
4. Dermatologist; Master's degree in Internal Medicine; Professor of the Service of Dermatology, HC-UFPR
5. Rheumatologist; Assistant Professor of Rheumatology, UFPR
Correspondence to: Scheila Fritsch. Rua Mauá, 360, apto 304 – Alto da Glória. CEP: 80030-200. Curitiba, PR, Brazil. E-mail: scheilaf@gmail.com

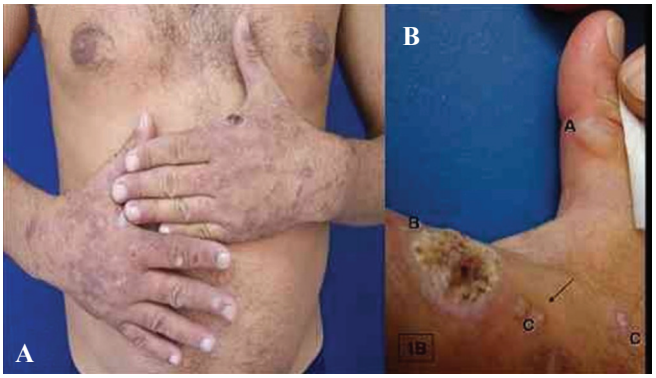

Figure 1
A) Erosions, scars and miliae on the dorsum of both hands. **B)** Close-up of the lesions. a) Intact tense blister with serous content in the left thumb; b) erythematous, crusted, eroded lesion following rupture of a blister; c) scarring lesions and cysts of milia on the dorsum of the left hand.

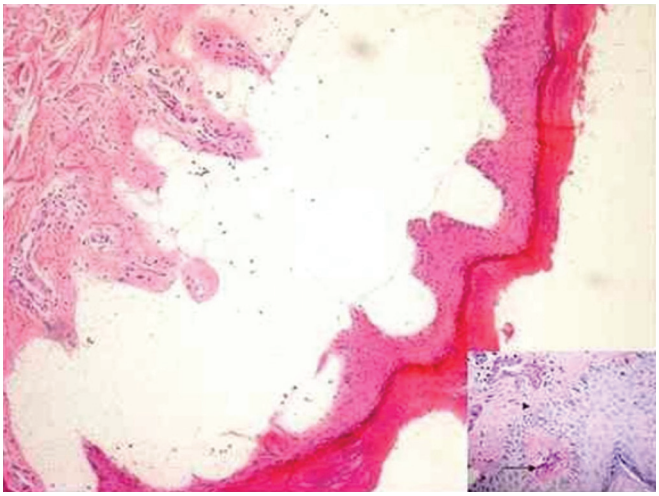

Figure 2
Porphyria cutanea tarda: skin with thick corneal layer over epidermis with irregular moderate acanthosis. Note the large subepidermal split, with undulating appearance of the dermal papillae that project into the blister. The blister shows scattered leukocytes and lymphocytes (HE, 100x). Close-up: deposition of PAS positive material in the vessel walls (arrow), and basement membrane with usual thickness (arrow head). (PAS with diastase digestion, 400x).

evidence of portal hypertension. He tested negative for hepatitis B and HIV, and his ferrogram was normal. Additional investigation revealed titers of antinuclear antibodies (ANA) of 1:640, speckled nuclear pattern, anti-RNP positivity, normal C3 level, consumed C4, and anti-DNA positivity (1:80). Renal biopsy evidenced mesangial proliferative glomerulonephritis, with immunofluorescence rich in granular deposits of IgG, IGA, and C3, and activity index of 4 and chronicity of 2. Because of high proteinuria, arterial hypertension, anti-DNA positivity, and complement consumption, monthly pulse therapy with cyclophosphamide and methylprednisolone (0.75 mg/m^2 and 1 g intravenous, respectively) was initiated. No reactivation of HCV was observed (quantitative CRP remained undetectable), and the proteinuria improved.

DISCUSSION

PCT, the most frequent type of porphyria, is caused by the deficiency of the enzyme uroporphyrinogen decarboxylase (UROD). The diagnosis is based on physical examination, urinary porphyrin excretion profile, and detection of isocoproporphyrin in the feces.[2] The lesions, restricted to sun-exposed areas, are mainly blisters that evolve to crusts and miliae, and heal in weeks to months, leaving atrophic or hyperpigmented areas. Hypertrichosis, sclerodermoid plaques, and scarring alopecia might be observed.[2] Microscopically, the skin shows subepidermal splits with undulating appearance of the dermal papillae that project into the splits. Sections stained with periodic acid Schiff (PAS) with diastase digestion show thickening of blood vessel walls in the superficial dermis, the most damaged site due to sun-exposure,[1] and perivascular lymphomononuclear infiltrates.[3] Immunofluorescence shows deposits of immunoglobulins, mainly IgG.[4] The severity of liver dysfunction, frequent in PCT, varies, mainly in the presence of alcohol abuse and/or iron overload. The pathophysiology of the disease can be explained by the accumulation of porphyrins in the skin, which are photosensitizing.[4] The molecules stimulated by light transfer energy to adjacent molecules, promoting the following: peroxidation of lipid membranes; oxidation of nucleic acids; action of porphyrins on complement activation; stimulation of polymorphonuclear cells; and collagen production induction by fibroblasts.[5] In addition to ultraviolet light, PCT is associated with other factors that contribute to inactivation/inhibition of the UROD enzyme, such as estrogens, alcohol, iron overload, HCV, and HIV. Treatment of SLE with hydroxychloroquine has precipitated PCT.[5] Disease control involves total protection from sun exposure, cessation of alcohol use, and discontinuation of estrogens. For patients with PCT and hemochromatosis, phlebotomy is the most adequate treatment. Patients with no iron overload might benefit from low doses of chloroquine (100−200 mg twice a week), because that drug mobilizes hepatic porphyrins, favoring their urinary excretion.

The skin lesions of SLE can be specific or unspecific.[6] Of the later, blistering lesions are rare (less than 5% of the cases),[7]

and should raise the suspicion of other entities, such as PCT, pemphigus, dermatitis herpetiformis, epidermolysis bullosa acquisita, and drug-induced lesions.[4,6,7] When the blisters are caused by lupus, they are usually chronic, disseminated, subepidermal, and leave no scar.[7]

Our patient had histology of mesangial proliferative or class II lupus nephritis,[8] which usually manifests as non-nephrotic proteinuria, no change in arterial blood pressure, in complement, and in renal function, and negativity for anti-DNA (differently from that observed in our case). The HCV, detected by use of serology and with an always negative quantitative CRP, can also trigger mesangial proliferative glomerulonephritis.[9] Because HCV does not explain the other findings of SLE in this patient, in addition to the possibility of a false positive anti-HCV, the renal findings were considered compatible with lupus nephritis. However, that virus could be related to the appearance of the PCT lesions in this patient.

PCT has already been associated with several autoimmune disorders. The largest case series already published about the association of PCT and SLE dates back to 1998.[5] In that cohort, of 676 patients with porphyria (all types), 2% had SLE, and most adult patients were in their forties. The diagnosis of SLE precedes that of porphyria in most reports,[5] differently from our case. Possible explanations for the coexistence of SLE and porphyrias have already been suggested by Harris et al.,[10] such as common genetic changes, porphyria as a trigger of autoimmune response, and metabolic errors triggered by SLE leading to porphyria. Regarding the first hypothesis, the gene for the UROD enzyme, which is impaired in PCT, is known to be in chromosome 1, and another region of that same chromosome, 1q41-q42, has already been implicated in the immunogenetics of SLE.[7] Another fact supporting a common pathogenesis is the simultaneous occurrence of those diseases in some patients.[5] The second hypothesis assumes that photostimulated porphyrins act upon immune cells, leading to cell damage and exposure of autoantigens. Despite being attractive, it does not explain all cases (since SLE can precede porphyria), and there is no significant increase in autoantibodies in patients with PCT.[5] To confirm the third hypothesis (SLE triggering porphyria), studies on the metabolic pathways of heme biosynthesis in patients with SLE would be necessary, but they do not exist in the literature. The occurrence of common risk factors, such as exposure to ultraviolet light and use of oral contraceptives, could explain only part of the cases.

Data defining whether the concomitance is pure coincidence or a true association of diseases still lack.[4,5] In addition, risk factors for the progress of one disease into the other are yet to be defined, as is those patients' prognosis. In addition to the male gender, would the association with PCT be another factor of severity for the systemic prognosis of SLE? This might explain why, although the renal biopsy showed class II nephritis, our patient had a more aggressive clinical and laboratory outcome than expected.

The association of PCT and SLE has therapeutic consequences. Sun protection should be emphasized, because the lesions of PCT are triggered by higher wavelengths than those of SLE.[5] The routine use of antimalarials in SLE can be a risk for PCT. That risk is dose-dependent, and several authors have contraindicated the daily administration of antimalarials indicated for SLE, because of the risk of massive porphyrinuria (fever, nausea and hepatocelular injury, including hepatic necrosis).[1,4,5,7] Thus, in cases of the association of PCT and SLE, low doses of antimalarials (half of the usual dose, only twice a week) are recommended.[4]

In clinical practice, a patient with lupus, significant photosensitivity and blistering lesions should always be assessed for porphyrias, because of the therapeutic implication of the association of those diseases.

REFERENCES

REFERÊNCIAS

1. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet 2010; 375(9718):924−7.
2. Frank J, Poblete-Gutiérrez P. Porphyria cutanea tarda − When skin meets liver. Best Pract Res Clin Gastroenterol 2010; 24(5):735–45.
3. Vieira FMJ, Aoki V, Oliveira ZNP, Martins JEC. Estudo da imunofluorescência direta, imunomapeamento e microscopia óptica na porfiria cutânea tarda. An Bras Dermatol 2010; 85(6):827–37.
4. van Tuyll van Serooskerken AMT, Habets JMW, Badeloe S, Poblete-Gutiérrez P, Frank J. Porphyria cutanea tarda in pre-existent lupus erythematosus – is there an association? Int J Dermatol 2007; 46(Suppl 3):50–2.
5. Gibson GE, McEvoy MT. Coexistence of lupus erythematosus and porphyria cutanea tarda in fifteen patients. J Am Acad Dermatol 1998; 38(4):569–73.
6. Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. Lupus 2010; 19(9):1050–70.
7. Haendchen L, Jordão JM, Haider O, Araújo F, Skare TL. Porfiria cutânea tarda e lúpus eritematoso sistêmico. An Bras Dermatol 2011; 86(1):173–5.
8. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB *et al*. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004; 15(2):241–50.
9. Akagi S, Sugiyama H, Makino H. Infection and chronic kidney disease. Nippon Rinsho 2008; 66(9):1794–8.
10. Harris MY, Mills GC, Levin WC. Coexistent systemic lupus erythematosus and porphyria. Arch Intern Med 1966; 117:425–8.