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DYSAUTONOMIA IN A CUTANEOUS POLYARTERITIS NODOSA PATIENT: EVIDENCE OF SYSTEMIC EVOLVING?

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ABSTRACT – *Objective:* We report a case of a patient with a cutaneous polyarteritis nodosa who developed dysautonomia and review this association's literature.

Case report: A 75-year-old male patient was admitted with a recent history of recurrent ulcers on his lower limbs. A skin biopsy showed leukocytoclastic vasculitis and fibrinoid necrosis in arterioles. Antinuclear antibodies were positive in a titer of 1:320, with other autoantibodies being negative. A cutaneous polyarthritis nodosa (cPAN) diagnosis was determined based on cutaneous ulcers, compatible histopathology, and the exclusion of systemic manifestations. Methotrexate, folic acid, colchicine, and one single dose of betamethasone depot were administered with a good response, gradually healing the ulcers. However, after two years, the patient felt some episodes of syncope. Orthostatic hypotension (110x80 mmHg standing and 50x30 mmHg in supine position) was noted, and a clinical diagnosis of dysautonomia was determined. Fludrocortisone was started, and the patient felt better.

Conclusions: This patient illustrates the first case of cutaneous polyarteritis nodosa, which evolved to pre-syncope and syncope episodes due to dysautonomia. The possibility of cPAN evolving into a systemic condition is discussed.

KEYWORDS: Dysauonomia, Vasculitis, Polyarteritis nodosa, Autonomous system.

INTRODUCTION

Cutaneous polyarteritis nodosa (cPAN) is a limited form of PAN (polyarteritis nodosa) that is considered to be a rare disease and accounts for 4% of all PAN cases[1]. Although called a benign form of PAN, it may have significant morbidity due to skin ulcerations, painful skin nodules, and digital infarcts; minor systemic symptoms may also develop, such as fever, arthralgia, and local neuropathy[1]. The evolution of cPAN to a systemic condition is uncommon, but it has been documented[2]. While considered idiopathic vasculitis, cPAN has been associated with infections like Streptococcus and hepatitis B and C virus[3]. In addition, inflammatory bowel disease has also been linked to cPAN[3].

Dysautonomia is a wide range of conditions that affect the autonomic nervous system[4,5]. It has been found in patients with peripheral neuropathies[6], with autoimmune blockade of the ganglionic autonomic transmission[7], as a paraneoplastic disease (more frequent with lung cancer)[8], or as a result of a hered-

itary problem among other conditions[9]. In addition, in patients with vasculitis, dysautonomia has been observed in autoimmune diseases such as Sjögren's syndrome, lupus, dermatomyositis, and Behçet's disease[10,11]. In this context, symptoms of orthostatic hypotension are commonly found and vary in severity from slight to debilitating. In rare cases, orthostatic hypotension has been linked to cardiovascular and cerebrovascular events[12].

Although classical PAN is a disease with a high prevalence of peripheral neuropathies (50% to 75% of patients)[13], neurological involvement in the cutaneous form is secondary to focal skin damage. Therefore, it should be localized within areas of skin lesions[14]. Consequently, one would not expect cPAN to be primarily linked to dysautonomia. We aimed at reporting the case of a patient with cPAN who evolved with dysautonomia.

CASE REPORT

A 75-year-old male patient, an ex-smoker, had a medical history of hepatosplenic schistosomiasis treated with oxaminiquine 20 years ago. In July 2016, he looked for medical attention with a recent history of recurrent painful ulcers of lower limbs and numb feet. He denied fever, weight loss, or arthritis. The physical examination demonstrated two ulcers on his left leg of about 3 cm in diameter each (Figure 1). Laboratory tests revealed normal blood cell count, negative cryoglobulins, and normal complement levels. Erythrocyte sedimentation rate (ESR) was 81 mm/1st hour [normal range (nr): < 20 mm/1st hour], and the C-reactive protein (CRP) 65 mg/L (nr: < 5mg/L). Antinuclear antibodies (ANA) were positive in a titer of 1:320 with a fine speckled pattern. Anti-Ro/SS-A, anti-La/SS-B, anti-dsDNA, anti-U1RNP, anti-Sm, ANCA, anti-CCP, rheumatoid factor, and antiphospholipid antibodies were absent. Serology for infectious diseases and schistosomiasis screening were negative. Thrombophilia studies were negative. Doppler venous and artery ultrasound of the lower limbs was interpreted as normal. A skin biopsy showed a moderate inflammatory infiltrate on the dermis, with mononuclear cells, neutrophils, and eosinophils; fibrinoid necrosis of the arterioles; and leukocytoclastic vasculitis. A diagnosis of cPAN was determined[15] based on

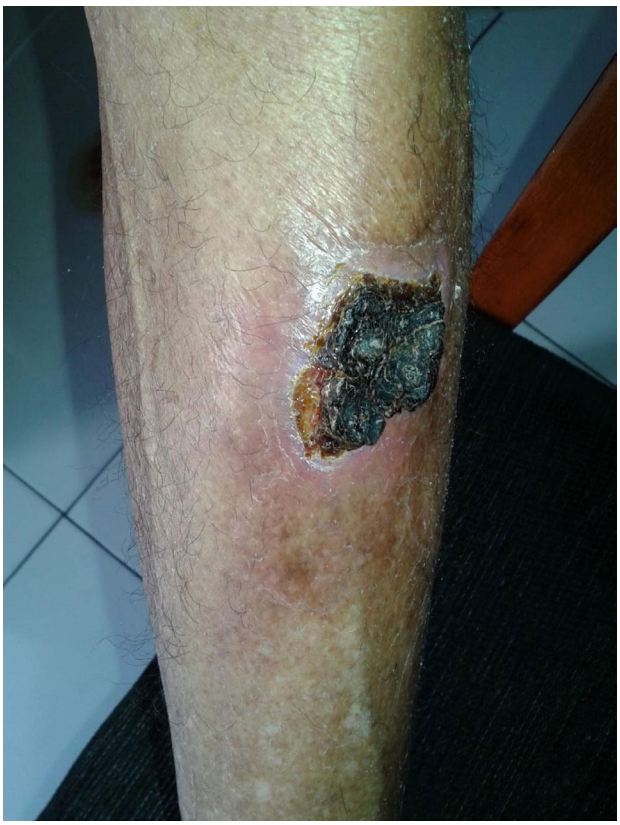

Figure 1. Leg ulcer in the patient with cutaneous polyarteritis nodosa (cPAN).

cutaneous ulcers, compatible histopathology, and the exclusion of systemic manifestations. Methotrexate (15 mg/week), colchicine, and a single dose of betamethasone depot were instituted. After five months, the patient was asymptomatic, all ulcers healed, ESR and CRP were normal, and a reduction of methotrexate and colchicine was initiated. After two years, he noted lightheadedness, pre-syncope, and syncope episodes. Orthostatic hypotension was detected (110x80 mmHg in standing and 50x30 mmHg in supine position), with a stable heart rate. No evidence of active clinical vasculitis was found, and no pupil or diaphoresis alterations were noted. ESR was 12 mm, and CRP was 4.93 mg/L. Echocardiogram and a Holter study were normal. Ambulatory monitoring of blood pressure showed several episodes of hypotension.

A diagnosis of hypotension secondary to dysautonomia was determined, and the patient was oriented to drink water abundantly and avoid prolonged standing. Fludrocortisone 0.1 mg/day was initiated, with a partial improvement. After increasing the dose to 0.2 mg twice a day, all the symptoms disappeared. Currently, he is oligosymptomatic without any evidence of active vasculitis and marked improvement of dysautonomia.

DISCUSSION

We report the first case of dysautonomia in a patient with cPAN. The orthostatic symptoms observed in this patient could not be attributed to a cardiovascular problem; other drugs than methotrexate and colchicine.

Some possible explanations as that dysautonomia are linked to neuropathy, and neurological involvement is quite frequent in classical PAN[13]. Then a possible evolution of the patient's cPAN to systemic disease could be hypothesized. Nevertheless, our previous study of 22 Brazilian patients with cPAN did not observe this transition[15]. Also, a Japanese study with 22 patients[14] and an American[16] with 79 cases verified that no cPAN form had progressed to systemic disease. Importantly, Chen[2] described that 2/20 cases of cPAN evolved to a systemic PAN after 18 and 19 years, and they were female and had peripheral neuropathy, positive ANA, and rheumatoid factor. Another possibility is that the two clinical situations were distinct entities linked by an autoimmune background. However, autoimmune diseases are known to coexist in the same individual. Moreover, autoimmune autonomic ganglionopathy with ganglionic nicotinic acetylcholine receptor autoantibodies is usually associated with subacute dysautonomia. These autoantibodies have been described in association with other autoimmune diseases such as Sjögren[17]. Unfortunately, the search for this autoantibody was not done in our case.

Our patient had a positive ANA that could concern the diagnosis of any other connective tissue disease. However, no clinical signs or autoantibodies to support a connective tissue disease diagnosis were detected. Of note, ANA positivity has been found in 3/22 patients from a Japanese series[14] and 23% in our Brazilian series[15] of cPAN.

CONCLUSIONS

This article describes the first case of cutaneous polyarteritis nodosa that developed dysautonomia characterized by orthostatic hypotension.

Ethics approval:
Ethical approval was not required.

Informed consent:
Informed consent was obtained from the patient.

Consent for publication:
Consent for publication was obtained from the patient.

Availability of data and material:
All data are available at request.

Conflict of interest:
The authors declare no conflict of interest.

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JFC: conceptions, supervision, writing, analysis, submission; TLS: writing, revision; YS: writing, revision.

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