Amantadine-induced livedo reticularis - Case report*

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Abstract: Livedo reticularis is a spastic-anatomical condition of the small vessels which translates morphologically by a reticular pattern, interspersing cyanosis, pallor and erythema. The same can be congenital or acquired. Among the acquired, we highlight the physiological livedo reticularis and the idiopathic livedo by vasospasm; the latter configures the most common cause. The drug-induced type is less common. The drugs amantadine and norepinephrine are often implicated. Cyanosis is usually reversible if the causative factor is removed, however, with chronicity, the vessels may become permanently dilated and telangiectatic. We report a case of a patient diagnosed with Parkinson's disease with chronic livedo reticularis associated with the use of amantadine and improvement after discontinuation of the drug.
Keywords: Amantadine; Livedo reticularis; Vascular diseases

INTRODUCTION

Livedo reticularis (LR) should be considered an elementary dermatological lesion, grouped within vascular macules, representing a finding of common dermatological clinical examination.[1] The term 'livedo', first suggested by Hebra to describe a purplish discoloration of the skin caused by an abnormality in the cutaneous circulation.[2]

LR is a physiological, vasospastic response of cutaneous microvasculature to cold or systemic disease. It is believed that the blood supply of normal skin is arranged in cones or hexagons, whose apex is composed of the cutaneous arteriole, based on the skin territory with a 1 cm by 4 cm area, depending on its blood irrigation. Situations where there is reduction of the circulatory flux of these arterioles or of venous drainage may lead to clinical appearance of LR.[3,4]

Erythematous-cyanotic well defined spots, called complete or closed are clinically observed, delimiting internal skin areas with normal aspect or pale in color. [1,3,4]

Semiologically, it is fundamental to know the difference from livedo racemosa, characteristically showing poorly defined slim and open lesions. This should direct clinical reasoning to pathological causes.[4]

LR is benign in most cases; however, it may be secondary to different disorders, especially in persistent cases. Vascular, rheumatological, endocrine or even infectious diseases are listed as possible causes, besides conditions that lead to blood hyperviscosity. Finally, certain rugs may be responsible for a LR clinical picture (Chart 1). [3]

We report the clinical case of a patient with Parkinson's disease, presenting chronic, persistent LR, associated with the use of antiparkinson medication.

CASE REPORT

A male, 79-year-old patient mentioned the onset of erythematous-bluish lesions of lacy aspect, predominantly on the lower limbs, aggravated by cold weather, for around three years. He denied local or systemic symptoms. Hypertensive, he was medicated with propranolol. He had a cerebral vascular accident 13 years ago. A Parkinson' disease patient, he uses amantadine in association with carbidopa and levodopa.

During physical examination were observed linear maculous lesions of erythematous-bluish color and lacy aspect on the lower limbs. No ulcerated lesions were evident, nor signs of atrophic scars (Figures 1 and 2).

The laboratory investigation included a com-

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Chart 1: Main causes of livedo reticularis

Congenital Livedo Reticularis:	Cutis marmorata telangiectatica congenita
Acquired Livedo Reticularis:	
- Vasospasms:	Primary livedo reticularis, collagenosis, Raynaud's disease.
- Reduction of flux:	Thrombocythemia, policythemia vera, cryoglobulinemia, cryofibrinogenemia, cold agglutinin , paraproteinaemia, antiphospholipid syndrome, deficiency of S and C proteins, antithrombin III, mutation of V Leiden factor, homocystinuria, hyperhomocysteinemia; disseminated intravascular coagulation, thrombotic thrombocytopenic purpura
- Pathology of vascular wall:	Polyarteritis nodosa, cryoglobulinemic vasculitis, vasculitis associated with autoimmune diseases, calciphylaxis, Sneddon's Syndrome, livedoid vasculopathy.
- Vascular obstruction:	Cholesterol piston, septic; atrial myxoma, trombosis, hyperoxaluria
- Infections:	Hepatitis C, *Mycoplasma pneumoniae*, Syphilis.
- Medications:	Noradrenaline, Interferon, Amantadine.

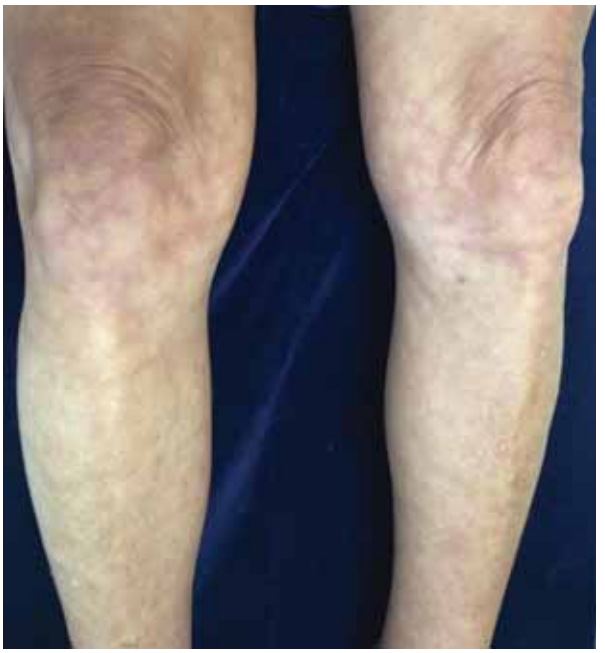

Figure 1: Livedo reticularis. Linear maculous lesions of erythematous-bluish color and lacy aspect on lower limbs

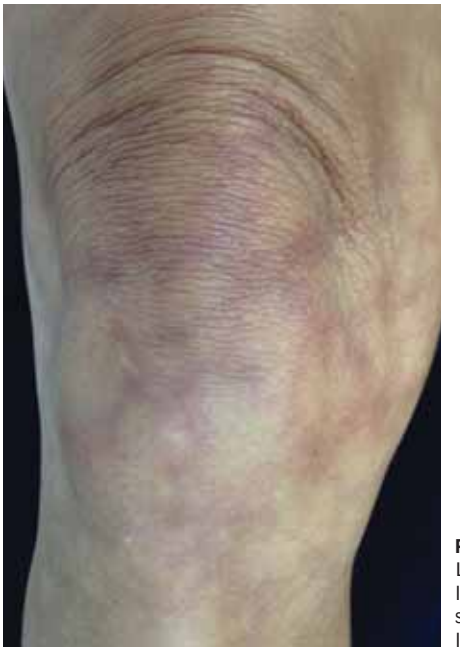

Figure 2: Livedo reticularis. Detail showing the lacy aspect

plete blood count, antinuclear factor (ANF), C3, C4, ENA profile, VDRL, rheumatoid factor, lupus anticoagulant, total proteins and fractions, TGO, TGP, VHS and serologies for hepatitis B and C, chest radiograph and EAS, without alterations.

The hypothesis of LR associated with the use of amantadine was considered and the patient was referred for neurological evaluation; the medication was suspended. Two months after the suspension, the patient did not present dermatological lesions anymore (Figure 3).

DISCUSSION

The etiological investigation of LR involves a detailed anamnesis with information regarding the use of medication, time of onset, associated symptoms, current diseases and recent surgeries. This physical examination is extremely important, as well as laboratory tests and histopathological examination that may suggest the etiology. LR is an adverse effect commonly described in patients using amantadine for treatment of Parkinson's disease, with preference for the female gender and involving mainly the trunk and lower limbs.[5] The differential diagnosis with livedo racemosa, with a pattern of irregular and incomplete circles

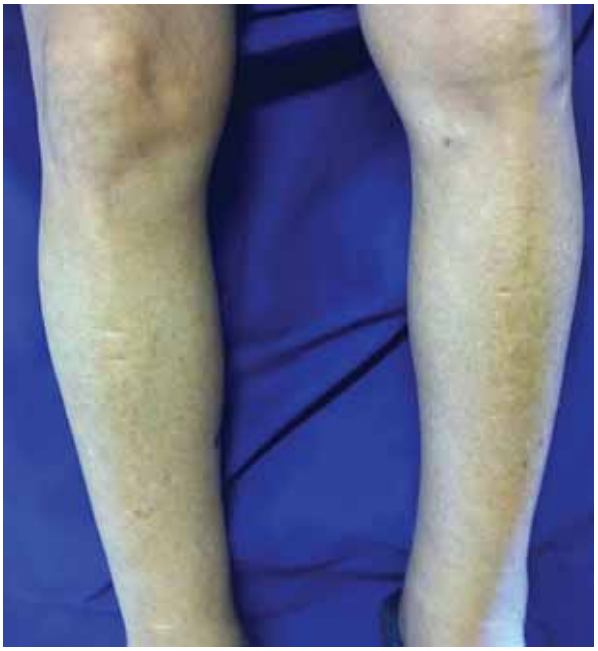

Figure 3: Two months after interruption of treatment with amantadine, the patient did not present livedo reticularis

and generalized involvement, should be considered. This is normally pathological and results from the local and persistent blood flow impediment, as by arteriosclerosis and Sneddon's syndrome.[4,6] Any case of livedo racemosa needs neurological investigation.

The skin is irrigated by arteries that are divided into arterioles at the junction of dermis and subcutaneous cellular tissue, forming the deep vascular plexus, which is parallel to the epidermis[1]. Arterioles emerge from this plexus and run perpendicularly to the epidermis, dividing into capillaries near the cutaneous surface, where they form the superficial vascular plexus.[3,5] A reduction in the volume of blood running in these arterioles may lead to LR.

Amantadine is one of the best known drugs that cause LR. Used at first as antiviral agent, today it is more commonly used in Parkinson's disease.[7] It is an adamantine derivative that stimulates norepinephrine and dopamine release into the synaptic cleft. [5] This drug has a anticholinergic effect and blocks N-methyl-D-aspartate (NMDA) receptors. [8] The physiopathology of LR stimulated by this drug is still not fully known, up to 40% of patients will present it.[3,8]

The amantadine-induced LR pattern suggests generalized cutaneous vascular alteration by the impact on arteries and arterioles of the dermis, corroborated by the absence of systemic involvement during the treatment. [5] It is a reversible side effect, with a variable clinical course (1 to 48 months). [5] Progression to ulceration is possible, but is usually rapidly resolved by withdrawing the drug. As amantadine significantly improves the neurological symptoms, especially dyskinesias derived from the use of levodopa, some patients opt for living with LR, which, except for the cutaneous manifestation, is asymptomatic. [5]

LR histopathology will depend on the basic cause. In the physiological or idiopathic forms, resulting from vasospasm, no alteration was found. When associated with a drug, the histopathological lesion examination usually shows absence of vasculitis and epidermis without alterations; is is not critical for diagnosis. [4,5,6,9]

It is important to call attention to this side effect of amantadine, as this association is not always noticed by doctors and this drug is frequently prescribed in the treatment of Parkinson's disease.❑

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