

## Case for diagnosis

### Caso para diagnóstico

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#### CASE REPORT

White female, 58 years old, retired clerk, suffering from Parkinson's disease and depression for three years, being treated with amantadine, pramipexole, paroxetine and lorazepam.

The patient reported that for previous two years she had noticed a lace-like reddish-violet discoloration of the skin when exposed to cold, particularly on the face, nasal apex, inner surface of the upper limbs, abdomen, breasts and legs. The condition grew steadily worse and over time adopted a fixed macular pattern.

The patient reported no other joint symptoms and denied hypertension, abortions or thrombotic episodes and no similar cases in the family. She denied travel outside of the city of Botucatu.

Dermatological exam showed coarse purplish lace-like discoloration on the inside of the upper limbs, extremities, face, abdomen, back and lower limbs (Figures 1, 2 and 3).

Tests: antinuclear factor, anti-RNP, anti-Sm, Anti-Jo1, anti-La, anti-Ro, c-ANCA, p-ANCA, rheumatoid factor, lupus anticoagulant, antiphospholipid, anti-cardiolipin, serologies for hepatitis and HIV, lactate dehydroge-

nase, creatinine, transaminases, complete blood count and serum protein electrophoresis, were all normal.

Histopathological examination revealed atrophy of the epidermis and mild perivascular lymphocytic infiltrate in the superficial dermis, without vasculitis or thrombi.



FIGURE 2: Livedo affecting the extremities



FIGURE 1: Lace-like cyanotic macular lesions on inside of the forearm

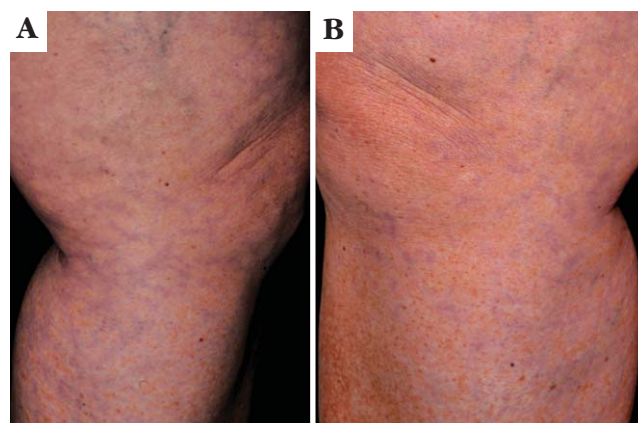


FIGURE 3: Livedo affecting the lower limbs: the inner side of left (A) and right (B) thigh

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## DISCUSSION

Livedo reticularis is a complex clinical syndrome caused by changes in skin blood flow in the arterioles and the outcome is common to various etiologies. Its lacy appearance is linked to the vascular anatomy of the skin (blood supply distributed in cones with 1-4 cm bases located on the skin surface). Each cone is supplied by an arteriole which is affected in the livedo, causing a mottled reticular pattern. The cyanotic appearance occurs in the anastomoses between the cones, caused by deoxygenated blood congestion.<sup>1,2</sup>

The most common form is idiopathic livedo reticularis which mainly affects children and young white women on the lower limbs. The condition is transient and often triggered by cold. The main causes of livedo are shown in table 1.<sup>2</sup>

The etiological investigation of livedo reticularis is a challenge for the clinician, involving a detailed clinical interview, a physical examination and laboratory tests to identify the acquired causes, plus a histopathological examination which may provide some indication of the etiology.<sup>2,3</sup>

Livedo reticularis and racemosa are known side effects in patients taking amantadine to treat Parkinson's disease. The incidence varies in the literature: from 2% to 90%, occurring predominantly in women and in the lower limbs.<sup>4-7</sup>

Amantadine is a symmetric amine derivative of the adamantane which boosts the release of norepinephrine and dopamine in nerve endings. The pathophysiology of amantadine-induced livedo is uncertain. According to

**TABLE 1:** Etiological classification of livedo reticularis

Physiological livedo reticularis	Sjogren's Syndrome
Cutis marmorata	Arteritis
Idiopathic or primary livedo reticularis	Polyarteritis nodosa
Congenital	Temporal arteritis
Cutis marmorata telangiectatica congenita (CMTC)	Systemic Lupus Erythematosus
Idiopathic acquired	Antiphospholipid antibody syndrome
Uncomplicated	Rheumatoid arthritis
With ulceration in winter	Dermatomyositis
With ulceration in summer	Lymphoma
With systemic vascular involvement	Pancreatitis
Secondary livedo reticularis	Infections
With vascular obstruction	TB
Stasis	Syphilis
Paralysis	Leprosy
Myocardial infarction	Hepatitis C
Occlusive disease	Brucellosis
Thromboembolisms	<i>Coxiella burnetti</i>
The bends (nitrogen bubbles)	Endocarditis
Cholesterol embolism	Meningococemia
Oxalosis (primary hyperoxaluria)	Endocrinological diseases
Thrombophilias	Hyperparathyroidism (hypercalcemia)
Disseminated intravascular coagulation	Calcifilaxia
Increased blood viscosity	Hypothyroidism
Polycythemia rubra vera	Cushing's disease
Thrombocythemia	Carcinoid syndrome
Cryoglobulinemia	Pheochromocytoma
Crioibrinogenemia	Nutritional
Cold agglutinins	Pellagra
Hypergammaglobulinemia	Letrogenic
Monoclonal gammopathy	Intraarterial bismuth
Vasculitis	Catecholamines (phenylephrine)
Microscopic polyangiitis	Amantadine
Livedoid Vasculitis	Quinidine
Arteriosclerosis	Asferamina
Sneddon Syndrome	Minocycline
Scleroderma	Pentazocine
Divry-Van Bogaert Syndrome	Nonsteroidal antiinflammatory drugs

the catecholaminergic theory these neurotransmitters generate effects on the peripheral circulation.<sup>1,8</sup>

Amantadine also inhibits the release of acetylcholine, decreasing the stimulation of the globus pallidus and substantia nigra in the subthalamic nucleus. NMDA receptors in the skin can also be stimulated by the drug.<sup>1,9</sup>

The diffuse pattern of amantadine-induced livedo suggests generalized vascular changes due to the scattered impact on the dermal vessels. This is corroborated by the absence of systemic involvement during treatment.<sup>7,8</sup>

Livedo is a reversible side effect of amantadine, with a slow clinical course (1-48 months). The disorder will therefore only abate after a long period following

suspension of the medication.<sup>8,9</sup>

Owing to the substantial improvement of the neurological symptoms with the use of amantadine, patients opt to live with livedo, which is asymptomatic (as in the case of the patient described above), or amantadine should be replaced by rimantadine.<sup>10</sup>

Although livedo reticularis is a known side effect of amantadine (leading to its reduced use in recent years) this association has neither been observed nor described by dermatologists. In view of the fact that amantadine is currently being increasingly employed to treat Parkinson's disease, the authors feel that it is important to draw the attention of clinicians, neurologists and dermatologists to the resurgence of this complication. □

**Abstract:** We report the case of a 58-year-old white female with Parkinson's disease. She evolved to an extensive livedo reticularis in the limbs and abdomen after commencing treatment with amantadine. We discuss the diagnostic approach to livedo reticularis and its differential diagnoses, emphasizing that the drug etiology must be considered when investigating livedo reticularis.

**Keywords:** Amantadine; Livedo reticularis; Parkinson's disease

**Resumo:** Descreve-se caso clínico de paciente feminina adulta, portadora de doença de Parkinson em uso de amantadina que desenvolveu extenso quadro de livedo reticular nos membros e abdome após o início do medicamento. Discutem-se a semiotécnica diagnóstica do livedo reticular e seus diferenciais. Os autores salientam que a etiologia medicamentosa deva ser considerada no diagnóstico dos livedos reticulares. **Palavras-chave:** Amantadina; Doença de Parkinson; Livedo reticular

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