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Case Report

Livedo reticularis following drug interaction of sertraline and amantadine in a patient with obsessive-compulsive disorder and depression: A brief report

Running Title: Livedo reicularis and amantadine

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Abstract

Livedo reticularis (LR) is a cutaneous vascular pattern that presents with reticular patch morphology. LR is a manifestation of a wide range of diseases, from idiopathic to systemic. We reported the clinical image of a patient with obsessive-compulsive disorder (OCD) and LR associated with amantadine use. On examination, mild postural tremor was left-handed and had a kinetic tremor. Rest tremor and re-emerge tremor were detected in addition to mild rigidity and bradykinesia in the patient; we proposed probable drug-induced Parkinsonism.

We should notice skin lesions after amantadine use and consider LR after the prescription of it. Also, co-administration of SSRIs and amantadine may increasethe probability of LR.

Keywords: Livedo reticularis; Amantadine; Obsessive-compulsive disorder; Sertraline

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Introduction

Livedo reticularis (LR) is defined as a physiological and vasospastic response of cutaneous microvasculature to a cold or systemic disease. LR affects the skin and appears as a lace-like purplish discoloration of the skin. The legs are often affected. LR may exacerbate when the temperature is cold. Erythematous-cyanotic well-defined spots, which are also known as complete or closed, are clinically found. These spots delimit internal skin areas with the normal aspect or pale in color (1).

In terms of etilolgy, LR is caused following an interruption in the blood flow of the dermal arteries. This interruption can be occured due to spasm, inflammation, or vascular obstruction, which is associated with diseases having varying etiologies and severities (2). In terms of semiology, it is nessecary to discover the difference between LR and erythematous-cyanotic well-defined spots. LR characteristically has poorly defined slim and open lesions (3).In most cases, LR is benign. Neverthelse, it may be developed following different disorders, especially in persistent cases. LR can be caused by enlarged veins and blocked blood flow leaving the veins. There are two kinds of LR, namely primary and secondary. The secondary form of LR is also called livedo racemosa. Exposure to cold, use of tobacco, and emotional upset can worsen primary LR. However, secondary LR is associated with various diseases, such as congenital (present at birth), reaction to some medicines, namely amantadine or interferon, blood vessel diseases such as polyarteritis nodosa and Raynaud phenomenon, abnormal proteins, antiphospholipid syndrome, hepatitis C, and paralysis.

Here, we reported the clinical image of a patient with obsessive-compulsive disorder (OCD) and LR, associated with amantadine use.

Case presentation

A female, 65-year-old right-handed patient with a diploma education and a history of severe OCD and depression for more than 30 years referred to a neuropsychiatric clinic for evaluation of neuropsychiatric symptoms, drug dose regulation and assessment of drug skin eruptions. She had no history of diabetes, dyslipidemia, and antiphospholipid antibody syndrome. In family history, her brother had a history of OCD. Over the past year, many family members died from COVID-19 infection disease, which has exacerbated the patient's grievances and increased the patient's symptoms. Her drug history during this period is listed in column 1 of **Table 1**.

Six months ago, the patient was suffering from forgetfulness and cognitive problems, referred to a neurology clinic. Neurological examination findings included mild bradykinesia, rigidity, and rest tremor. MMSE (Mini-Mental State Examination) test was performed, and a score of 28 out of 30 was obtained, and those two scores decreased from the Delay recall (DR) part. Finally, mild cognitive impairment was diagnosed, and in this period, she was taking some drugs listed in column 2 of **Table 1**.

Table 1. Drugs that were administered for patient in different times

Diagnosis	OCD + MDD	Mild Cognitive Impairment (MCI) + OCD + MDD	OCD + MDD
Time	**10 years ago**	**6 month ago**	**1 month ago**
Drugs history	Clomipramine, 25 mg/TDS	Sertraline, 100 mg/Daily	Clomipramine, 37.5 mg/at night
	Depakine, 500 mg/Daily	Clomipramine, 37.5 mg/Daily	Sertraline, 150 mg/Daily
	Fluvoxamine, 100 mg/BD	Trifluoperazine, 4 mg/ Daily (1 mg, II-II-0)	Aripiprazole, 5mg/Daily
	Risperidone, 1mg/Daily	Lorazepam, 0.5 mg/Daily	Amantadine, 100 mg/BD
	Chlorodiazepoxide, 10mg/Daily	Amantadine, 100 mg/Daily	Lorazepam has been discontinued because of hypersomnia and overselation
		Atorvastatin, 10 mg/Daily	
		Ginkgo biloba, 1 mg/Daily	

OCD: Obsessive-compulsive disorder; MDD: Major depressive disorder; TDS: Three times a day; BD: Twice a day.

Vitamin B12 level was 629 mcg, triglyceride 198 mg/dl, liver function test (LFT), and homocysteine were in the normal range. The patient was referred to a sports clinic for exercise therapy.

The recent visit showed a relative improvement in OCD and depression symptoms, but there was a significant obsessional idea yet. Also, the patient and her husband complained of memorizing and repeating sentences with sleep disturbance, but her performance for housework was intact On examination, mild postural tremor is left-handed and has a kinetic tremor. Rest tremor and re-emerge tremor were detected in addition to mild rigidity and bradykinesia in the patient; we proposed probable drug-induced Parkinsonism.

The medications for the last month are listed in column 3 of **Table1**, which 25 mg of sertraline has been added to previous medications. Two weeks ago, after taking 25 mg of sertraline, the patient suffered from a series of generalized lesions in the area from the hands to the shoulders (**Figure 1 A and B**) and the legs to the knees (**Figure 1 C**), which led to the possibility of livedo reticularis with amantadine. Finally, the patient was referred to a dermatologist.

Laboratory tests

The findings are listed in **Table2**.

Table 2. Labratory tests 2

Lab tests	Serum level
Vitamin B12	629 mcg
Liver function test	Normal
Triglyceride	198 mg/dl
Homocysteine	Normal

Imaging findings

Three months before intervention MRI was performed, and damage related to periventricular ischemia was reported. One month ago intervention, the MRI findings also showed mild bilateral Frontoparietal atrophy,the medial temporal lobe atrophy (MTA) score (Scheltons' scale)was zero.

Skin biopsy

The dermatologist took a biopsy and confirmed that it was because of amantadine. Therefore, the patient stopped taking amantadine. After two weeks of stopping amantadine, lesions were reduced by about 20% but not yet disappeared.

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Follow amantadine discontinuation, rate and frequency of tremor were not increased. Only the obsession of the person has intensified, to the extent that she washes for about 6 hours. It is important to attend to the side effect of amantadine. Sertraline is an inhibitor of liver enzymes, and it increases the serum level of amantadine.Aeven with a smaller amount of amantadine, this complication occurs.

Amantadine-induced LR is highly variable, ranging from 2% to 90%, and is more common in women than men (1). The appearance of LR subsides with the discontinuation of the drug (4).

We listed other drugs related to drug-induced LR in (**Table 3**).

Table 3. Medications associated with LR

Amantadine
Minocycline
Diphenhydramine
Gemcitabine
Heparin
Thrombolytics
Interferon beta
Erythromycin/lovastatin interaction
Catecholamines
Bismuth
Quinidine
Arsphenamine

Conclusion

We should refer to skin lesions using follow amantadine and consider the possibility of Livedo Reticulris after its administration. Concomitant use of SSRIs and amantadine may also increase the risk of Livedo reticularis. Therefore, physicians and specialists should be careful in prescribing these two types of drugs simultaneously.

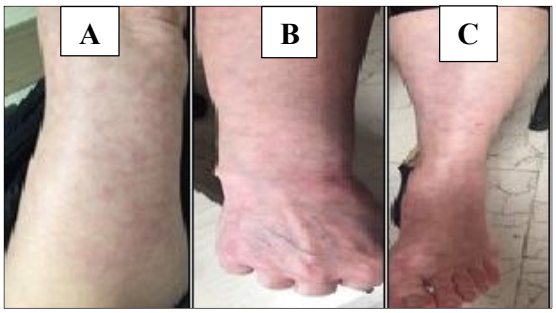

Figure 1. A:Livedo reticularis. Linear macular lesions with bluish erythematous color and lace aspect on upper limbs (From wrist to elbow). B: Livedo reticularis. Linear maculous lesions of erythematous-bluish color and lacy aspect on lower limbs (From elbow) C: Livedo reticularis. Linear maculous lesions of erythematous-bluish color and lacy aspect on lower limbs.

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