CASE REPORT

Psychiatry and Clinical Psychopharmacology 2023;33(3):218-221
DOI:10.5152/pcp.2023.23712

Sertraline-Induced Leukocytoclastic Vasculitis with Definite Causal Association: A Case Report

Mahmut Selçuk

Department of Psychiatry, Muğla Sıtkı Koçman University, Faculty of Medicine, Menteşe, Muğla

ABSTRACT

Antidepressants like sertraline are frequently used to treat psychiatric diseases like depression, panic disorder, and obsessive-compulsive disorder. Small-vessel vasculitis called leukocytoclastic vasculitis is defined histopathologically by immune complex-mediated vasculitis of the dermal capillaries and venules. Typically, it shows up as purpura on the lower extremities, either with or without systemic involvement. Leukocytoclastic vasculitis can be idiopathic but it can also happen in conjunction with several medications. Here, we present data on sertraline-induced leukocytoclastic vasculitis in a patient with major depressive disorder. To our knowledge, sertraline and other selective serotonin reuptake inhibitors have not previously been definitively linked to leukocytoclastic vasculitis, which is rare with antidepressants.

ARTICLE HISTORY

Received: May 08, 2023
Accepted: May 23, 2023
Publication Date: August 7, 2023

INTRODUCTION

Vasculitis is a diverse collection of diseases characterized by blood vessel inflammation.[1] A typical type of small-vessel vasculitis is known histopathologically as leukocytoclastic vasculitis (LCV). Dermal capillaries and venules that have immune complex deposition are characteristic of cutaneous lesions associated with LCV.[1] Extracutaneous symptoms of cutaneous LCV are uncommon and only occur in about 70% of patients.[1,2]

Leukocytoclastic vasculitis can be idiopathic, but it can also be linked to neoplasms, autoimmune diseases, infections, and specific drugs.[2] Tumor necrosis factor inhibitors, rituximab, statins, antithyroid medications, and immune checkpoint inhibitors have been proven to be the medications most frequently linked to LCV.[2,3] Moreover, a small number of LCV cases have been linked to psychiatric medications such as paroxetine,[4] trazodone,[5] maprotiline,[6] fluvoxamine,[7] and clozapine.[8]

In the treatment of the major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder, sertraline is one of the most widely used selective serotonin reuptake inhibitors (SSRIs) and one of the best-tolerated antidepressants.[9] Here, we present a patient with depressive symptoms who developed severe vasculitis after using sertraline. For this case study, the patient gave written informed consent.

CASE PRESENTATION

Our patient was a 50-year-old female who applied to our outpatient psychiatry clinic with symptoms of sadness, emptiness, tiredness, lack of energy, and loss of interest in normal daily activities. Her complaints had been present for about 2 months, during which time these symptoms occurred most of the day and nearly every day. We diagnosed the patient with major depressive disorder according to the diagnostic and statistical manual-5 (DSM-5) diagnostic criteria and started treatment with 50 mg/day of sertraline. One week after treatment began, she developed cutaneous eruptions limited to her hands. She stopped the drug immediately after the lesions erupted. One week after she stopped the drug, the lesions regressed. Two weeks later, since the patient was hesitant to stop sertraline for fear of aggravating her depression, she resumed taking it but at half the dose. In the following 2 days, she continued developing new lesions in her both hands and feet. The reported skin rashes were verified at her next appointment. In both her upper and lower extremities, the patient developed a pruritic rash with red, maculopapular lesions that were 1-5 mm in diameter. She was physically examined and found to have palpable purpura on her hands (Figure 1) and feet (Figure 2). Her body temperature was normal, her heartbeat was regular at 84 beats per minute, and her arterial blood pressure was 120/70 mmHg. She disclaimed having a fever, a viral infection

Corresponding author: Mahmut Selçuk, e-mail: mahmutselcuk@gmail.com

Cite this article as: Selçuk M. Sertraline-induced leukocytoclastic vasculitis with definite causal association: A case report. *Psychiatry Clin Psychopharmacol*. 2023;33(3):218-221.

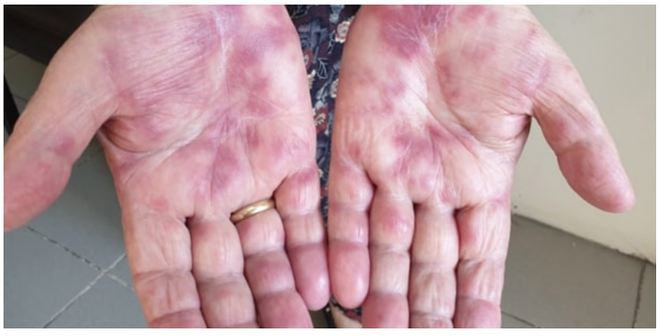

Figure 1. Palpable non-blanching purpura on both hands.

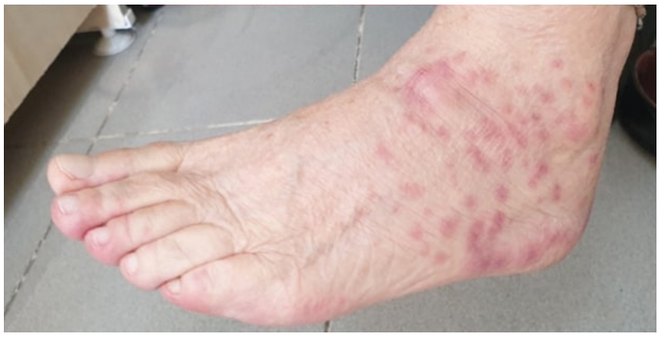

Figure 2. Palpable non-blanching purpura on feet.

that had occurred previously, arthritis, allergies, and any respiratory, gastrointestinal, or urinary symptoms. There was no evidence of abdominal discomfort, lymphadenopathy, hepatosplenomegaly, or abnormal heart–lung or lymphatic examination results.

We referred the patient to the dermatology clinic, and a dermatologist suspected a diagnosis of vasculitis. In favor of an LCV diagnosis, a skin biopsy was performed that revealed characteristic perivascular neutrophilic and eosinophilic infiltrates, and the presence of inflammatory cells in the vessel wall was observed (Figure 3).

Her workup was significant for elevated erythrocyte sedimentation rate 36 (0–20 mm/h), C-reactive protein 6.5 (0.0-0.7 mg/dL), myoglobin, and creatinine kinase. The levels of immunoglobulin, complement component 3, and complement component 4 were all within normal ranges. Autoantibodies (anti-nuclear antibodies and anti-neutrophil cytoplasmic antibodies), platelet count, and serological testing for hepatitis B and C viruses were all within normal limits. Hematuria, proteinuria, and granular casts were not detected in the urine analysis. The occult blood test on feces came out negative. The radiograph of the chest was normal. No more organs were impacted. She was diagnosed with single-organ, skin-isolated, small-vessel vasculitis, often known as LCV without systemic vasculitis or glomerulonephritis. The dermatologist advised symptomatic treatment with antihistamines and topical corticosteroid cream. We stopped the suspected agent sertraline and started the patient on 10 mg/day of vortioxetine. The pruritus and cutaneous lesions began to subside a few days after drug cessation. Symptoms had completely resolved in 3 weeks and did not appear again.

MAIN POINTS

- Leukocytoclastic vasculitis (LCV) is the histological term for a typical form of small-vessel vasculitis.
- Leukocytoclastic vasculitis may be idiopathic, although it may also be connected to neoplasms, autoimmune disorders, infections, and certain medications.
- There have been a few LCV cases linked to psychiatric medications such as paroxetine, trazodone, maprotiline, fluvoxamine, and clozapine, however, sertraline has never been definitively linked to LCV, which is rare with antidepressants.
- Here, we describe a case of a patient with depressive symptoms who, after taking sertraline, developed severe LCV.
- The patient's Naranjo Score was 9, indicating a definite causal association between the sertraline treatment and LCV.

DISCUSSION

The American College of Rheumatology's (ACR) established criteria for cutaneous small vessel vasculitis were met by our patient. According to the ACR classification criteria, cutaneous small-vessel vasculitis must have 3 of the following 5 symptoms to be diagnosed: (i) being older than 16 years of age at the onset of the disease, (ii) a history of taking a drug at onset as a suspected factor, (iii) the existence of palpable purpura, (iv) the existence of a maculopapular rash, and (v) a biopsy characterized by deposition of granulocytes around an arteriole.[10]

In this case, the temporal relationship of the lesions with the use of sertraline, the regression of the lesions after the discontinuation of sertraline, and the reappearance of the skin rash with the resumption of the drug suggest

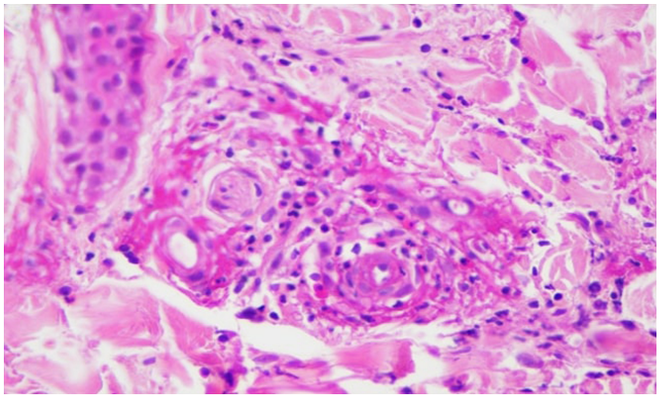

Figure 3. Hematoxylin and eosin staining (×400): in the dermis, inflammation rich in eosinophils and neutrophils is observed around the vessel and nerve sheath, and the presence of inflammatory cells in the vessel wall and erythrocyte extravasation in the adjacent dermis is observed.

that sertraline might be the causal agent for the cutaneous vasculitis.

Infectious agents, medications, and vaccines have all been implicated as potential causes of vasculitis, even though its etiology and pathogenesis are still poorly understood.[10] We were unable to identify any unusual standard laboratory results or health issues in the patient's past that might have been connected to any other potential causes of vasculitis. Sertraline was therefore thought to be the only factor that could have caused vasculitis in this case. The Naranjo Adverse Drug Reaction Probability Scale (hereafter "Naranjo Score") result was 9, indicating a definite causal association.[11,12]

Different antidepressants have rarely been associated with cutaneous vasculitis.[6,7,10] To our knowledge, no SSRIs and other antidepressants have had a Naranjo Score that indicates definite causation with vasculitis, previously. In a recently reported case of sertraline-related vasculitis,[9] the Naranjo Score was 6, which indicated a probable association with sertraline.[12] Although our case study is the second in this area, it must be stated that our patient's vasculitis was in a definite causal relationship with sertraline treatment. Our patient stopped taking her medication after the vasculitis appeared in her hands, but she started sertraline again on her own decision shortly after the lesions improved; thus, the lesions were renewed on the hands and moreover also appeared on the feet. This situation raised the Naranjo Score to a level indicating a definite causal association in our case study, which differed from that recently published report that suggested a probable association between sertraline usage and cutaneous vasculitis.[9]

There are 10 questions in the Naranjo Score, and the answers might be "Yes," "No," or "Do not know." For each response, a different point value (-1, 0, +1, or +2) is given. Total scores can range from -4 to +13; a reaction is considered definite if it is a 9 or higher, probable if it is a 5 to 8 or higher, possible if it is a 1 to 4, and doubtful if it is a score of 0 or less.[11,12] Below is a condensed list of the 10 questions and our patient's scale points:

- Have there been any conclusive reports of this reaction in the past? (+1)
- Did the side effect occur after the medication was administered? (+2)
- Did stopping the medication or administering a particular antagonist cause an improvement in the adverse reaction? (+1)
- Did the adverse reaction come back after you administered the medication again? (+2)
- Were there any further potential causes for the reaction? (+2)
- Did the adverse reaction return after receiving the placebo? (0)
- Were toxic quantities of the drug found in the blood or other fluids? (0)
- Upon increasing the dose, did the reaction get worse? Or did the response become milder as the dose was reduced? (+1)
- Did the patient previously experience similar responses to the medication or a related drug? (0)
- Was the adverse event confirmed by any other objective evidence? (0)

Leukocytoclastic vasculitis usually occurs 1–3 weeks after initiating the drug.[2] Although the precise pathophysiology of drug-induced LCV is yet unknown, it appears to be an immune-related response to a precipitating antigen, such as a drug.[2] According to the available literature, the inducer medication may function as a hapten, promoting the creation of antibodies and immunological complexes that trigger the typical complement cascade. Polymorphonuclear leucocytes are drawn to this cascade (i.e., neutrophils and basophils). Vascular injury results from induced leukocytes secreting lysosomal enzymes that compromise the capillary venules' structural and functional integrity. This causes perceptible purpura as a result of heavy leucocytic infiltration, edema, and diapedesis of erythrocytes.[7,13]

If LCV is detected, it should be looked into to determine if the condition is limited to the skin or if it is a component of a systemic vasculitis.[3] Fever is one of the most frequently reported systemic symptoms; other possible causes include arthritis, the gastrointestinal tract, or the kidneys. Detailed examinations should be made for all the body areas mentioned.[3]

The priority in the treatment of LCV depends on the reason for the rash. It is crucial to stop using the suspected agent immediately. Specific treatment may not be required for those with mild diseases. For cutaneous symptoms, topical anti-inflammatory drugs might be utilized. Systemic anti-inflammatory medications (such as nonsteroidal anti-inflammatory drugs or corticosteroids) or immunosuppressive agents should be used in the treatment of systemic involvement.[14,15]

Fortunately, because an offending drug was identified in the presented case, discontinuing it resulted in the improvement of the lesions. The prognosis was good. Systemic involvement was absent.

In conclusion, it is critical that medical professionals are informed about the potential cutaneous adverse effects of sertraline and other SSRIs.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The author has no conflict of interest to declare.

Funding: The author declared that this study has received no financial support.

REFERENCES

1. Frumholtz L, Laurent-Roussel S, Lipsker D, Terrier B. Cutaneous vasculitis: Review on diagnosis and clinicopathologic correlations. *Clin Rev Allergy Immunol*. 2021;61(2):181-193. [CrossRef]
2. Baigrie D, Goyal A, Crane JS. *Leukocytoclastic Vasculitis*; In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2018.
3. Fraticelli P, Benfaremo D, Gabrielli A. Diagnosis and management of leukocytoclastic vasculitis. *Intern Emerg Med*. 2021;16(4):831-841. [CrossRef]
4. Margolese HC, Chouinard G, Beauclair L, Rubino M. Cutaneous vasculitis induced by paroxetine. *Am J Psychiatry*. 2001;158(3):497-497. [CrossRef]
5. Kimyai-Asadi A, Harris JC, Nousari HC. Critical overview: Adverse cutaneous reactions to psychotropic medications. *J Clin Psychiatry*. 1999;60(10):714-25; quiz 726. [CrossRef]
6. Oakley AMM, Hodge L. Cutaneous vasculitis from maprotiline. *Aust N Z J Med*. 1985;15(2):256-257. [CrossRef]
7. Eren I, Çivi I, Şahin M. Cutaneous leucocytoclastic vasculitis associated with fluvoxamine. *Bull Clin Psychopharmacol*. 2008;18(4):306-308.
8. Mukherjee S, Era N, Mukherjee M, Tripathi SK. Leukocytoclastic vasculitis secondary to clozapine. *Indian J Psychiatry*. 2019;61(1):94-96. [CrossRef]
9. Fatima R, Acharya A, Bozorgnia F, Garg A, Altorok N. Sertraline-associated immunoglobulin A vasculitis. *Am J Ther*. 2022;29(4):484-486. [CrossRef]
10. Chembolli L. Drug-induced cutaneous small vessel vasculitis following vortioxetine. *J Skin Sex Transm Dis*. 2021;4(1):139-142. [CrossRef]
11. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. [CrossRef]
12. Kose S, Akin E, Çetin M. Adverse drug reactions and causality: The Turkish version of Naranjo Adverse Drug Reactions Probability Scale (Turkish version). *Psychiatry and Clinical Psychopharmacology*. 2017;27(2):205-206. [CrossRef]
13. Buchberger R, Wagner W. Fluvoxamine: Safety profile in extensive post-marketing surveillance. *Pharmacopsychiatry*. 2002;35(3):101-108. [CrossRef]
14. Bliss SA, Warnock JK. Psychiatric medications: Adverse cutaneous drug reactions. *Clin Dermatol*. 2013;31(1):101-109. [CrossRef]
15. Fan PT, Davis JA, Somer T, Kaplan L, Bluestone R. A clinical approach to systemic vasculitis. *Semin Arthritis Rheum*. 1980;9(4):248-304. [CrossRef]