Sertraline induced Leukocytoclastic Vasculitis, a Case Report, and Review Literature

Angkana Norasetthada

Department of Internal medicine, rheumatology unit, Buddhachinaraj Phitsanulok Hospital, Thailand.

Introduction

A rare secondary small vessel vasculitis characterized by inflammation of blood vessels caused by various drugs, including antibiotics, anti-tumor necrosis factor-alpha agents, immunotherapeutic drugs, and psychoactive agents. The skin is most commonly affected, but other tissues and organs, such as the subcutis, kidneys, or lungs, may also be involved. Systemic disease develops only in a minority of patients, typically when treated with the causative drug over a prolonged period of time. Presenting signs and symptoms include skin rash, myalgia, arthralgia, fever, and malaise.[1]

Drug-induced vasculitis is a diagnosis of exclusion. There is no laboratory diagnostic tool for drug-induced vasculitis. Eosinophil count may be raised, this is seen more frequently in the case of systemic involvement. A comprehensive drug history of prescribed and over-the-counter medicine is paramount. Tissue biopsy can be beneficial in confirming the diagnosis.[1] The disease entity ranges from relatively benign symptoms requiring supportive care to life-threatening episodes requiring intensive care. The etiologies of vasculitis include autoimmune syndromes, infectious agents, and medications.[2,3] The association of drug therapy with development of cutaneous vasculitis is recognized with numerous therapeutic agents. In fact, it has been estimated that 10–20% of dermal reactions to drugs are vasculitic reactions. Systemic manifestations have been less well reported, even though patients have commonly described nonspecific symptoms such as fever, arthralgia, malaise, and lymphadenopathy.[4]

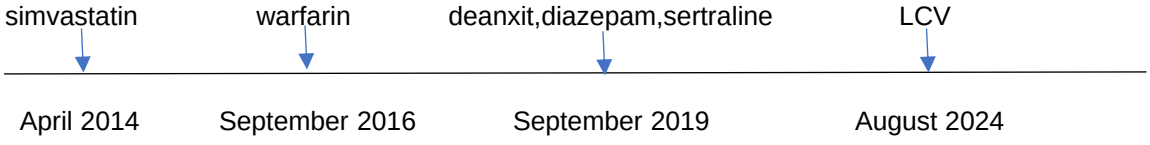
In the treatment of the major depressive disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder, sertraline is one of the most widely used selective serotonin reuptake inhibitors (SSRIs) and one of the best-tolerated antidepressants.[5] Here, I present a patient with depressive disorder who developed severe cutaneous vasculitis after using sertraline. For this case study, the patient gave written informed consent.

Case Presentation

This 78-year-old female was referred to Buddhachinaraj Hospital at the outpatient rheumatology clinic due to numerous palpable non-blanching purpura on both arms, thighs, legs, and trunk 26 days ago, on 21 August 2024. She disclaimed a fever, a viral infection that had occurred previously, arthritis, allergies, and any respiratory, gastrointestinal, or urinary symptoms, red eye, oral or genital ulcer.

Her medicines were simvastatin 20 mg due to dyslipidemia since April 2014, warfarin 3 mg due to paroxysmal atrial fibrillation since September 2016, sertraline 50 mg, diazepam 5 mg and deanxit (melitracen 10 mg+ flupentixol 0.5 mg) 1 tab per day due to depressive and sleep disorder since September 2019.

Timeline of medications used



She was physically examined and found to have an enormous number of palpable purpura on both arms, thighs, legs, and trunk (Figure1). Her body temperature was normal, her heartbeat was regular at 80 beats per minute, and her arterial blood pressure was 120/70 mmHg. There was no evidence of abdominal discomfort, lymphadenopathy, hepatosplenomegaly, or abnormal heart–lung or lymphatic examination results.

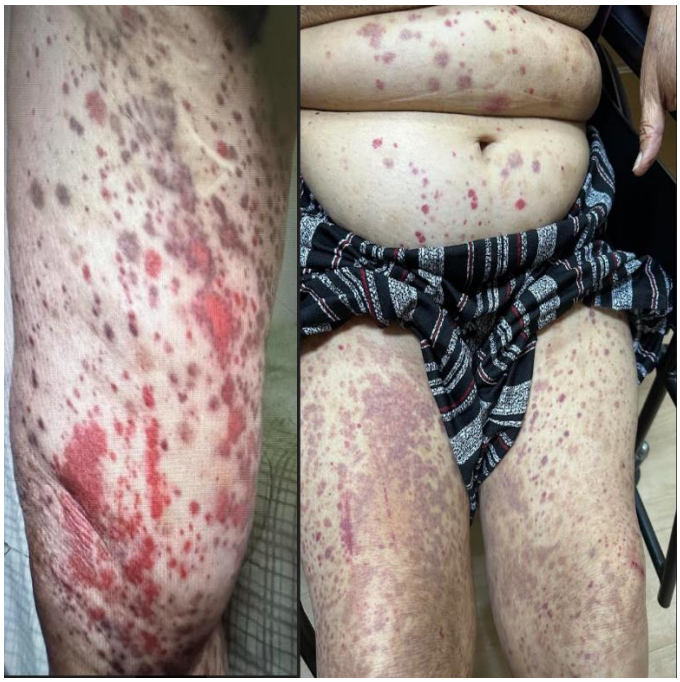


Figure 1 Palpable purpura on, thighs, legs and trunk.

Her laboratory investigations were significant for elevated C-reactive protein 40.1 mg/L (<5 mg/dl). The levels of complement component 3, and complement component 4 were all within normal ranges. Autoantibodies (anti-nuclear antibodies and antineutrophilic cytoplasmic antibodies), and serological testing for hepatitis B and C, HIV virus, anti-cardiolipin, included β2 glycoprotein antibodies were all negative. Hematuria, proteinuria, and granular casts were not detected in the urine analysis. Complete blood count, thyroid and liver function test were within normal limit. The INR was 1.40. The radiograph of the chest was normal. No more organs were impacted. Electrocardiography revealed normal sinus rhythm, no ST-T change, no chamber enlargement. Echocardiogram shown good LV contraction, LVEF 73% without RWMA, no valvular dysfunction, no LV dilatation, no pulmonary arterial hypertension, no intracardiac thrombus, and normal pericardium.

It was suspected a diagnosis of vasculitis. In favor of a leukocytoclastic vasculitis (LCV) diagnosis, a skin biopsy was performed that revealed a dense superficial and mid perivascular mixed inflammatory cells infiltrated that was composed of lymphohistiocytic, neutrophils, nuclear dust, and extravasated red blood cells, compatible with LCV (Figure 2). Direct immunofluorescent resulted; IgG, IgM, IgA, C3 and fibrin were all negative.

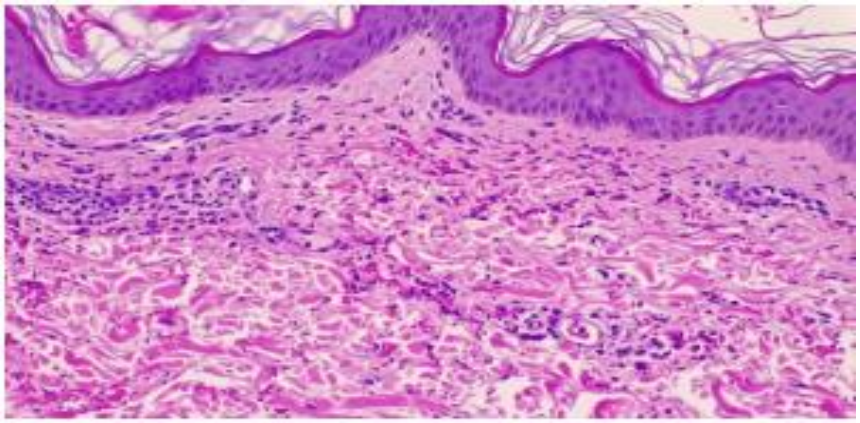


Figure 2 Skin biopsy; hematoxylin and eosin staining revealed a dense superficial and mid perivascular mixed inflammatory cells infiltrate that was composed of lymphohistiocytis, neutrophils,nuclear dust, and extravasated red blood cells

She was diagnosed with single-organ, skin-isolated, small vessel vasculitis, often known as LCV without systemic vasculitis or glomerulonephritis. Symptomatic treatment with antihistamines, topical corticosteroid cream, and withheld the suspected agent, sertraline was commencement. One week after she withheld sertraline, all the lesions had subsided leaving post-inflammatory hyperpigmentation. Two days later she had symptoms of sadness, tiredness, anorexia, loss of interest in normal daily activities and often crying. Then she resumed taking it. In the following 2 days, she developed new lesions in her thighs, legs, and trunk. Then mirtazapine (the other class of anti-depressant) was prescribed instead of sertraline. Two weeks later, all skin lesions were cleared, leaving only hyperpigmented lesions (figure 3), and her mood was improved.

Figure 3 palpable purpura on both arms, hands, thighs, legs and trunk were cleared, leaving only hyperpigmented lesions

Discussion

The American College of Rheumatology's (ACR) established criteria for cutaneous small vessel vasculitis were met by this patient. According to the ACR classification criteria, drug-induced 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.[6]

The most frequently implicated agents are propylthiouracil, dilantin, quinidine, sulfonamides, penicillins, and allopurinol. Other causes of LCV are infectious (15-20%), secondary to autoimmune diseases (15-20%), or paraneoplastic disease (5%). No identifiable cause can be detected in up to 45-55% of cases.[7]

This patient had no evidence of infectious, lymphoproliferative, or autoimmune disease, and the negative immunofluorescence finding do not support the latter either. 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 suggested that sertraline might be the causal agent for the cutaneous vasculitis. Sertraline was therefore thought to be the only factor that could have caused vasculitis in this case. The Naranjo Adverse Drug Reactions (ADRs) Probability Scale (hereafter "Naranjo Score") result was 9, indicating a definite causal association.[8,9] SSRIs are widely used for the treatment of depressive and anxiety disorders because of their low frequency of adverse reactions. They represent 70% of the total of antidepressants prescribed.[10]

In addition to SSRIs, the other class of antidepressants are;

- Serotonin-noradrenaline reuptake inhibitors (SNRIs), examples of SNRIs include duloxetine and venlafaxine.
- Noradrenaline and specific serotonergic antidepressants (NASSAs), for example mirtazapine.
- Tricyclic antidepressants (TCAs) examples included amitriptyline, clomipramine, dosulepin, imipramine, lofepramine, and nortriptyline.
- Serotonin antagonists and reuptake inhibitors (SARIs), for example, trazodone.
- Monoamine oxidase inhibitors (MAOIs), examples included, tranylcypromine, phenelzine, and isocarboxazid
- Serotonin modulator, for example, vortioxetin.

Almost all SSRIs antidepressive drugs have been reported to induce LCV, as follows: sertraline.[11,12], escitalopram.[13], citalopram[14], Paroxetine[15], fluvoxamine[16], After stopping fluvoxamine and switching to paroxetine vasculitis still occurred.[13,14] Different SSRIs could be involved in eliciting a similar allergic reaction. Such reported cross-reactivity was observed in the patient, as a class effect due to the SSRI active ingredient.[13,14,17]

The non-SSRIs group induced LCV as well, thus; duloxetine (SNRI)[18], vortioxetine (serotonin modulator)[19], maprotiline (TCA), and trazodone (SARI).[20] Hence antidepressants for this patient should not be SSRIs, SNRIs, serotonin modulators, or TCA.

The duration between exposure to a causative agent and subsequent development of vasculitis is extremely variable, ranging from hours to years. It is, therefore, difficult to ascertain an exact period after which drug-induced vasculitis is likely to commonly manifest. In most instances, however, the onset of drug-induced vasculitis typically occurs from 1 to 3 weeks after drug initiation. SSRI-induced ADRs may be dose-independent and therefore can occur early in treatment.[16] It is imperative for clinicians to be aware that drug-induced vasculitis can occur after increasing the dose of a medication, any time of drug use, or a re-challenge of the offending drug.[21]

The variable and often prolonged time course between commencement of propylthiouracil therapy and initial vasculitic symptoms was 3 days-7 years, 6 months-13 years after initiating treatment with hydralazine, 2 years for propranolol, 4 weeks for warfarin, sertraline was 1 week- 2 months[11-15,21] In this case the interval between the first administration of sertraline and the development of vasculitis was about 5 years. A dose-dependent reaction has been suggested in some case reports, although this is not consistent across the spectrum of drugs. Due to the potential severity of these reactions,

there is a paucity of data to show the recurrence of symptoms on re-challenge with the suspected drug.[22]

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. According to the available literatures, 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.[16,23]

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.[24,25,26]

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

Conclusion

It is critical that medical professionals are informed about the potential cutaneous adverse effects of sertraline and other SSRIs and advisable in such cases to substitute other classes of antidepressants for other non-related family of medications.

To cite: Norasetthada A.
Thai J Rheum. 2025;2(1):37-43. Available from: https://he04.tci-thaijo.org/index.php/tjr

References

1. Radić M, Martinović Kaliterna D, Radić J. Drug-induced vasculitis: a clinical and pathological review. Neth J Med. 2012 Jan;70(1):12-7.
2. Jennette JC, Falk RJ, Andrassy D, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an International Consensus Conference. Arthritis Rheum. 1994;37:87-92.
3. Dubost JJ, Souteyrand P, Sauvezie B. Drug- induced vasculitides. Baillieres Clin Rheumatol.1991;5(1):119-38.
4. Ekenstam E, Callen JP. Cutaneous leukocytoclastic vasculitis. Clinical and laboratory features of 82 patients seen in private practice. Arch Dermatol.1984;120:484-9.
5. Fatima R, Acharya A, Bozorgnia F, Garg A, Altorok N. Sertraline-associated immunoglobulin A vasculitis. Am J Ther. 2022;29(4):484-486.
6. Fraticelli P, Benfaremo D, Gabrielli A. Diagnosis and management of leukocytoclastic vasculitis. Intern Emerg Med. 2021;16(4):831-841.
7. Fiorentino DF. Cutaneous vasculitis. J Am Acad Dermatol. 2003; 48:311-40.
8. 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.
9. 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.
10. Baldessarini RJ. Drugs and the treatment of psychiatric disorders: depression and mania. In: Hardman JG, Limbird LE, Gilman, AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics.New York: The Mc Graw Hill Companies, Inc;1996:431-59.
11. Selçuk M. Sertraline-Induced Leukocytoclastic Vasculitis with Definite Causal Association: A Case Report. Psychiatry and Clinical Psychopharmacology 2023;33(3):218-221.
12. Fatima R, Acharya A, Bozorgnia F, Garg A, Altorok N. Sertraline-associated immunoglobulin A vasculitis. Am J Ther. 2022;29(4):484-486.
13. Flores- Suárez LF, Vega- Memije ME, Chanussot- Deprez C, Cutaneous Vasculitis During Selective Serotonin Reuptake Inhibitor Therapy The American Journal of Medicine. 2006;119(10):811-908.
14. Richard MA, Fiszenson F, Jreissati M, Jean Pastor MJ, Grob JJ. Toxi dermie aux antidepresseurs sérotoninergiques: 2 cas. Ann Dermatol Venereol. 2001;128:759-61.
15. Margolese HC, Chouinard G, Beauclair L, Rubino M. Cutaneous vasculitis induced by paroxetine. Am J Psychiatry. 2001;158(3):497-497.
16. Eren I, Çivi I, Şahin M. Cutaneous leucocytoclastic vasculitis associated with fluvoxamine(SSRI). Bull Clin Psychopharmacol. 2008;18(4):306-308.
17. Warnock JK, Morris DW. Adverse cutaneous reactions to antidepressants. Am J Clin Dermatol 2002;3(5):329–39.
18. Erfan G, Albayrak S, Oguz K, Kayayci S, Oznur M, et al. Leukocytoclastic vasculitis due to duloxetine. European Jornal of Dermatology. 2015;25:194-195.
19. Chembolli L. Drug- induced cutaneous small vessel vasculitis follow vortioxetine. (serotonin modurator) Journal of skin and sexually transmitted diseases. 2020;33:87-91.
20. Oakley AMM. , Hodge L. Cutaneous vasculitis from maprotiline. Aust N Z J Med. 1985;15(2):256-257.
21. ten Holder SM, Joy MS, Falk RJ. Cutaneous and systemic manifestations of drug- induced vasculitis. Ann Pharmacother. 2002;36:130–47.
22. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med. 1997;337:1512–23.
23. Buchberger R, Wagner W. Fluvoxamine: Safety profile in extensive post- marketing surveillance. Pharmacopsychiatry. 2002;35(3):101-108.
24. Fraticelli P, Benfaremo D, Gabrielli A. Diagnosis and management of leukocytoclastic vasculitis. Intern Emerg Med. 2021;16(4):831-841.

25. Bliss SA, Warnock JK. Psychiatric medications: Adverse cutaneous drug reactions. Clin Dermatol. 2013;31(1):101-109.
26. Fan PT, Davis JA, Somer T, Kaplan L, Bluestone R. A clinical approach to systemic vasculitis. Semin Arthritis Rheum. 1980;9(4):248-304.