

## VALPROATE-ACID-INDUCED CUTANEOUS LEUKOCYTOCLASTIC VASCULITIS

Davor Lasić<sup>1</sup>, Ranka Ivanišević<sup>2</sup>, Boran Uglešić<sup>1</sup>,  
Marija Žuljan Cvitanović<sup>1</sup>, Dubravka Glučina<sup>2</sup> & Ivana Hlevnjak<sup>2</sup>

<sup>1</sup>University Psychiatric Clinic, Clinical Hospital Centre Split, Croatia

<sup>2</sup>Department of Dermatology and Venerology, Clinical Hospital Centre Split, Croatia

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### INTRODUCTION

Vasculitis is an inflammatory disease of blood vessels characterized by the alteration or destruction of the vessel wall. There are three subtypes of vasculitis according to Chapel Hill Consensus Conference definition: Large Vessel Vasculitis, Medium-Sized Vessel Vasculitis and Small Vessel Vasculitis. Drug-induced vasculitis is usually Small Vessel Vasculitis represented as Leukocytoclastic Vasculitis. Leukocytoclastic Vasculitis is relatively common, with an incidence of 20:100 000 yearly. There are no age or sex predictions. The key event is the deposition of immune complexes in the walls of the capillaries and venules. In most cases, the process is a type III immune complex-mediated reaction according to the Gell and Coombs's classification of hypersensitivity reactions. Typical triggers for acute disease include infections and drugs, while recurrent disease is usually associated with hepatitis C infection, collagen-vascular disorders, hematological diseases or malignancy.

The cutaneous features of leukocytoclastic vasculitis are highly variable and may change rapidly. Almost all eruptions are symmetric, and the legs are most heavily involved. There is often swelling and pain. Mucosal surfaces are spared. The following clinical patterns can be seen, with wide degrees of overlap: hemorrhagic type, hemorrhagic-necrotic type, papulonecrotic type, polymorphous-nodular type, annular type, pustular type and urticarial type.

Leukocytoclastic vasculitis can also occur internally. It may affect certain organs, usually the kidneys or portions of the gastrointestinal tract, though the heart, lungs, and nervous system can also be involved. It can also occur in the joints.

There are no significant differences in clinical presentation, serologic abnormalities, and pathologic findings with the idiopathic forms of vasculitis.

Skin lesions are characterized by leukocytoclasia and fibrinoid necrosis of the blood vessels.

The classic manifestation is destruction of the small blood vessels in the papillary dermis. There is exocytosis of erythrocytes, accumulations of neutrophils with

nuclear dust, or debris (leukocytoclasia), fibrin deposition in the vessels wall and focal necrosis of the dermis. Early lesions may be dominated by lymphocytes and have little vessel destruction; late lesions may show primarily necrosis.

Early lesions almost always have intra- and perivascular deposition of C3, IgG and IgM. The outlook varies with the presence of associated disorders or known triggers. Leukocytoclastic vasculitis associated with medications or infections resolves rapidly when the responsible agent is removed.

Treatment of leukocytoclastic vasculitis can vary depending on the patient's situation.

The most important is to remove possible triggers and to treat any underlying disorder. A patient generally does better with avoidance of standing, resting in bed, elevation of the legs, and compression bandaging of the lower aspects of the legs. Topical therapy revealed application of High-potency corticosteroid creams under occlusion and may be helpful in treating early lesions. For mild recurrent or persistent disease, colchicine and dapsone are first-choice agents. Severe cutaneous and systemic disease requires more potent immunosuppression (prednisone plus azathioprine, methotrexate, cyclophosphamide, cyclosporine, or mycophenolate mofetil).

Valproic acid (VPA) is a chemical compound and an acid that has found clinical use as an anticonvulsant and mood-stabilizing drug, primarily in the treatment of epilepsy, bipolar disorder, and, less commonly, atypical depression with hypersomnia. It is also used to treat migraine headaches and schizophrenia.

Dermatological side effects of psychopharmacological drugs are most common in group of mood stabilizers and antiepileptic drugs, especially related with carbamazepine and lamotrigine.

Valproic acid has been associated with stomatitis and cutaneous leukoclastic vasculitis. A case of psoriasiform eruption has been reported in a patient receiving valproic acid. Dermatologic side effects including transient alopecia (2.6-12%), thinning of the hair, hair color changes, hair texture changes, and rare rashes have been reported. Valproic acid has been

implicated in producing Stevens-Johnson syndrome and Toxic epidermal necrolysis (TEN). Allergic reactions such as rashes are less common with valproic acid and other forms of valproate than with most other anti-epileptic drugs.

## CASE REPORT

A 35-year-old woman presented with purpuric papules on her lower extremities. She had, as she told, the same symptoms few months before but they spontaneously vanished. This time the skin lesions were persistent and they did not provoke itch, were not painful and the patient was not febrile. The patient has been on continuous anticonvulsive therapy for epilepsy since she was three years old. Since she was twenty she has been taking Rivotril (clonazepam) at the dosage of 2 mg. Three years ago, because of the worsening of epilepsy, her neurologist prescribed her Lamictal (lamotrigine) at initial dosage. At that occasion she developed exanthema accompanied with itch, so lamotrigine was withdrawn and replaced with Depakine Chrono (valproate) at dosage of 300 mg per day. A urinalysis with microscopy showed microscopic hematuria during this whole time she has been taking valproate (25-30E), and has been thrombocytopenic. The haematologist thought that the skin lesions were provoked by valproate. After taking minucious medical history, laboratory evaluation and examination, dermatologist diagnosed her valproate-induced vasculitis. She prescribed her Aeries (disloratadine) at dosage of 5 mg per day and topical corticosteroids on the lesion. During the follow-up period of seven days clinical features were the same, so Decortin (prednisone) at dosage of 20 mg per day and Peptoran (ranitidine) at dosage of 75 mg per day were prescribed.

Because of the need for the further examination the patient was admitted to the Department of Dermatology and Venerology, University Hospital Centre Split.

During the hospitalisation any possibility of systemic involvement was excluded. Kidney and liver function tests were within the normal range. C3 level was normal, and antinuclear and antineutrophil antibodies were absent.

A skin biopsy from the purpuric vesicular patch revealed perivascular cellular infiltration. Dense perivascular lymphohistiocytic infiltration with fibrinoid deposition in the vascular wall, red blood cell extravasation, nuclear dust, and endothelial swelling were observed revealing leukocytoclastic vasculitis. Conspicuous eosinophils were evident in the dermis. The lesions showed obvious improvement after discontinuing the valproate followed by the administration of 10 mg prednisolone daily for 2 weeks.

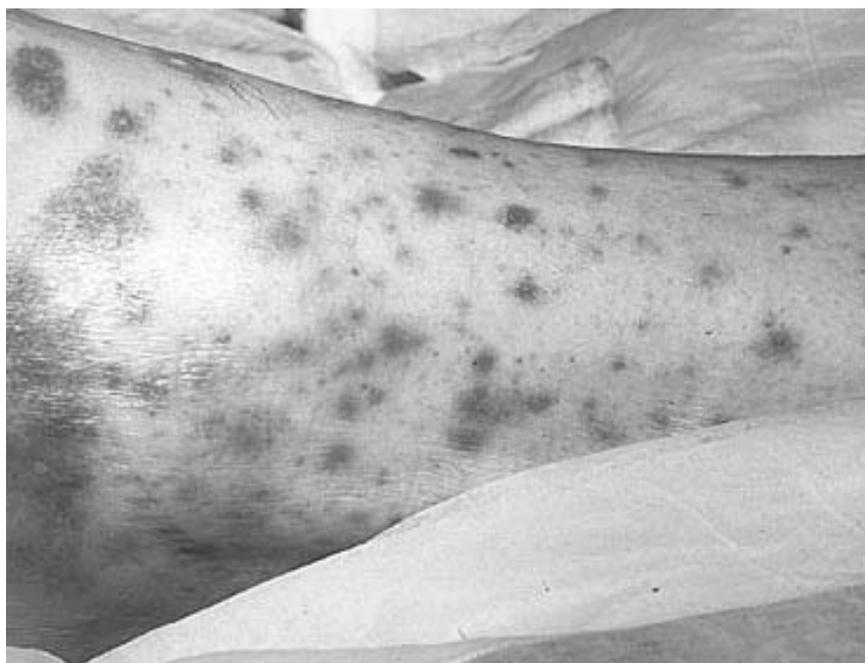
Corticosteroid therapy with decortine contributed to significant improvement of the skin lesions.

The patient was advised to consult her neurologist to evaluate the further antiepileptic therapy.

## DISCUSSION

Clinical recognition of drug-induced vasculitic is very important because continued use of the offending drug can lead to irreversible and life-threatening vasculitic organ damage (e.g. end-stage renal disease or pulmonary haemorrhage). Withdrawal of the drug often leads to spontaneous recovery, meaning that immunosuppressive therapy can be avoided.

The differential diagnosis between drug-induced and idiopathic vasculitic conditions may be difficult in the individual patient.



**Figure 1.** Leukocytoclastic vasculitis

**Table 1.** Medications associated with drug-induced vasculitis

ANTIBIOTICS	
	Cephotaxime
	Minocycline
	Anti-thyroid drugs
	Benzylthiouracil
	Carbimazole
	Methimazole
	Prophythiouracil
ANTI-TUMOR NECROSIS FACTOR- $\alpha$ AGENTS	
	Adalimumab
	Etanercept
	Infliximab
PSYCHOACTIVE AGENTS	
	Clozapine
	Thioridazine
MISCELLANEOUS DRUGS	
	Allopurinol
	D-Penicillamine
	Hydralazine
	Levamisole
	Phenytoin
	Sulfasalazine

Drugs found to be most frequently associated with vasculitis were propylthiouracil, hydralazine, colony-stimulating factors, allopurinol, cefaclor, minocycline, D-penicillamine, phenytoin, isotretinoin, and methotrexate (Table 1). The interval between the first exposure and appearance of symptoms was reported to be extremely variable (hours to years). Vasculitis has occurred after drug dosage increases and after rechallenge with the suspected drug. In the majority of cases, vasculitis has resolved after discontinuing the drug. Patients with more severe, often life-threatening, manifestations have required treatment with corticosteroids, plasmapheresis, hemodialysis, or cyclophosphamide. Death was the result in 10% of all published cases, with a predominance in patients in whom multiple organ systems were involved.

Since clinical presentation as well as serological and pathological parameters is identical to idiopathic forms of vasculitis, a high index of suspicion is necessary to

accurately and expeditiously diagnose drug-induced vasculitis.

Drug-induced vasculitis represents approximately 10% of acute cutaneous vasculitis cases and is difficult to diagnose. Diagnosis and assessment of an underlying cause of a drug includes an analysis of features such as timing of drug exposure, onset, course of reaction, and nature of a recurrent eruption on rechallenge.

There are laboratory markers that can help distinguish drug induced vasculitis from idiopathic autoimmune diseases, and a thorough knowledge about such serological changes may help to differentiate drug-induced from idiopathic syndromes (summarized in Table 2).

Allergic reactions such as rashes are less common with valproic acid and other forms of valproate than with most other antiepileptic drugs. Valproate-induced vasculitis is seen as an adverse drug reaction in ratio that is less than 1/ 1000. Tennis P. & Stern RS. found no confirmed serious cutaneous diagnoses in 1 504 new valproate users, during their record linkage study.

Diverse histological findings are noticeable, based on the inflammation period, red blood cell extravasation, nuclear dust, and endothelial swelling are suggestive findings of vasculitis. At least two histological components must occur to diagnose vasculitis: a perivascular inflammatory cell infiltrate and evidence of vascular injury. Necrosis of the vessel wall with deposition of fibrinoid material is a pathognomonic finding of vasculitis.

Biopsy is the gold standard for the diagnosis of cutaneous vasculitis and also necessary for the detection of cutaneous vascular immune complexes by direct immunofluorescence. Based on the type of vessel disrupted by inflammation (small and/or muscular), the distribution of vasculitis in the dermis and subcutis, and predominate inflammatory cell-type mediating vessel wall damage, a list of relevant differential diagnoses can be generated. This histologic information coupled with extravascular findings such as tissue eosinophilia, tissue neutrophilia, and/or granulomas, plus pathophysiologic markers such as direct immunofluorescent examination for immune complexes and serologic evaluation for antineutrophil cytoplasmic antibodies allows for more accurate diagnosis of specific vasculitic entities.

**Table 2.** Laboratory marker differences between drug-induced vasculitis and idiopathic systemic lupus erythematosus and ANCA associated vasculitis

	Drug-Induced Vasculitis	SLE	AAV
Antihistone abs.	Can be seen	Rare	Absent
AntidsDNA abs.	Absent	Common	Absent
ANCA	Common <sup>a</sup>	Rare	Common <sup>b</sup>
Antiphospholipid abs.	Common	Common	Rare
Immune complexes	Rare	Common	Absent

SLE, systemic lupus erythematosus; AAV, anti-neutrophil cytoplasmic antibodies-associated vasculitis;

a Multispecific; b Single ANCA specificity

## CONCLUSION

Each psychopharmac, regardless of its administration safety and the positive clinical experiences, can pose a potential risk of side effects. Allergic reactions such as rashes are less common with valproic acid and other forms of valproate than with most other antiepileptic drugs. Valproate-induced vasculitis is seen as an adverse drug reaction in ratio that is less than 1/1000. Leukocytoclastic vasculitis can also occur internally. It may affect certain organs, usually the kidneys or portions of the gastrointestinal tract, though the heart, lungs, and nervous system can also be involved. The clinician should be aware of uncommon but not rare possibility that a cutaneous eruption could evolve into a significantly more serious reaction.

Dermatological side effects are fortunately very rare but they should be constantly kept in mind.

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**Conflict of interest :** None to declare.

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Correspondence:

Davor Lasić, MD, PhD

University Psychiatric Clinic; Clinical Hospital Centre Split

Spinčićeva 1, 21 000 Split, Croatia

E-mail: dlasic@kbsplit.hr