

Leukocytoclastic Vasculitis Secondary to Pyridostigmine (Mestinon): Report of a Possible First Case

Gunveen Singh; Tim Hodgson, MBChB; David E Clarke, MD, FCCP

Perm J 2017;21:15-240

E-pub: 11/18/2016

<https://doi.org/10.7812/TPP/15-240>

ABSTRACT

Introduction: Pyridostigmine is an acetylcholinesterase inhibitor commonly used in the treatment of myasthenia gravis. We describe a patient who developed a rash after recently being started on pyridostigmine and give a general review of leukocytoclastic vasculitis.

Case Presentation: A 91-year-old man was diagnosed with ocular myasthenia gravis. He was started on pyridostigmine, and 2 weeks later he developed a rash. The rash was biopsied and found to be secondary to leukocytoclastic vasculitis; the pyridostigmine was stopped, loratadine was started, and the rash resolved.

Discussion: Leukocytoclastic vasculitis is commonly caused by a hypersensitivity reaction to medications, or it can be associated with certain medical conditions. We present a brief review of the most common medications and medical conditions known to cause this reaction, but to our knowledge this is the first description of pyridostigmine causing this reaction.

CASE PRESENTATION

A 91-year-old white man with ocular myasthenia gravis (confirmed by normal limb electromyography testing and a positive acetylcholine receptor antibody titer) was started on 30 mg twice daily pyridostigmine. Approximately 2 weeks later, he noticed a rash on his lower legs, but he did not seek immediate medical attention. He presented to the hospital several days later after a mechanical fall. During this hospitalization, bilateral palpable purpura were appreciated on the extensor surfaces of his lower legs (Figures 1 and 2). A punch biopsy of the rash was performed. Microscopy revealed a mixed inflammatory cell infiltrate with prominent neutrophils, associated nuclear dust, and red blood cell extravasation,

INTRODUCTION

Leukocytoclastic vasculitis (LCV) is an inflammatory reaction involving arterioles and venules of the skin. Other terms used to describe this disorder include cutaneous leukocytoclastic angiitis and hypersensitivity vasculitis. LCV typically presents as palpable purpura, but it may also present with urticarial-like lesions, petechial ulcers, erythematous plaques, or nodules. Its manifestations are primarily cutaneous; however, systemic findings such as fever, arthralgias, lymphadenopathy, and renal and hepatic dysfunction can occur.¹ The typical histologic findings in the dermis include a perivascular neutrophilic infiltrate with karyorrhexis (nuclear dust), variable numbers of mononuclear cells and eosinophils, fibrinoid necrosis, and extravasation of red blood cells. The pathogenesis of LCV has been suggested to be immune complex mediated.^{2,3} Numerous precipitating factors have been implicated in the development of LCV, with most cases being associated with drugs and infections.^{3,4}

This case report examines the possibility of a heretofore unknown relationship between pyridostigmine (Mestinon; Valeant, Laval, Quebec, Canada) and LCV.



Figure 1. Purpuric lesions on the extensor surface of the left leg.



Figure 2. Purpuric lesions on the extensor surface with associated ulceration on the lateral aspect of the right leg.

Gunveen Singh is a Medical Student in Internal Medicine at the University of Otago School of Medicine in Dunedin, New Zealand. E-mail: singu331@student.otago.ac.nz. **Tim Hodgson, MBChB**, is the Pathology Registrar at the University of Otago School of Medicine in Dunedin, New Zealand. E-mail: tim.hodgson@scslabs.co.nz. **David E Clarke, MD, FCCP**, is a Consultant in Medicine at The Dunedin Hospital; an Honorary Clinical Senior Lecturer at the University of Otago School of Medicine in Dunedin, New Zealand; Clinical Assistant Professor of Medicine at Stanford University School of Medicine; and a Hospitalist at the Santa Clara Medical Center in CA. E-mail: davidclarkemd@mac.com.

consistent with LCV (Figure 3). The epidermis was normal. Immunofluorescence studies were negative for immunoglobulin IgA, IgG, IgM, C3c, and fibrinogen. A histologic diagnosis of LCV was confirmed.

The patient had underlying atrial fibrillation, hypertension, and hyperlipidemia as well as a known ascending aortic aneurysm with an anterior-posterior diameter of 4.9 cm. He had had a stroke 7 years earlier with no residual neurologic sequelae. His medications upon admission to the hospital included bendrofluzide, canadersartan, simvastatin, warfarin, and pyridostigmine. The only medication change in the 2 years before his hospital admission had been the initiation of pyridostigmine approximately 2 weeks before his current hospital admission. There were no systemic symptoms or signs to suggest systemic involvement of the LCV.

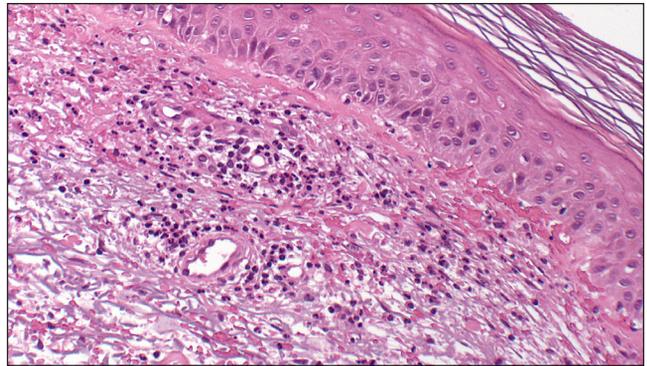
Laboratory blood tests revealed the following values: hemoglobin: 102 g/L; platelet count: $219 \times 10^9/L$; C-reactive protein: 20 mg/dL; erythrocyte sedimentation rate: 10 mm/hr; white blood cell count: $4.8 \times 10^9/L$; neutrophil count: $3.8 \times 10^9/L$; lymphocyte count: $0.5 \times 10^9/L$; monocyte count: $0.3 \times 10^9/L$; eosinophil count: $0.2 \times 10^9/L$; albumin: 35 g/dL; serum globulin: 30 g/L; and total serum protein: 65 g/dL. Liver function tests were normal and a viral hepatitis screen was negative. Anti-Sm antibodies, anti-RNP antibodies, anti-SS-A antibodies, anti-SS-B antibodies, anti-Jo-1 antibodies, anti-SCI-70 antibodies, antineutrophil cytoplasmic antibodies, anti-CCP antibodies, cryoglobulins, and rheumatoid factor studies were all normal. Serum protein electrophoresis revealed slightly elevated light chains with a normal kappa/lambda ratio, consistent with an inflammatory state.

Mestinon was discontinued and loratadine was started. The LCV gradually regressed during the ensuing month. Subsequent therapy for myasthenia gravis was not initiated because the ocular myasthenia gravis did not recur.

DISCUSSION

LCV is commonly caused by a hypersensitivity reaction to drugs. Although penicillins, cephalosporins, allopurinol, sulphonamides, and phenytoin are some of the most commonly implicated drugs, many other drugs or agents can cause LCV

Figure 3. Punch biopsy of skin showing features of leukocytoclastic vasculitis (perivascular mixed inflammatory infiltrate with prominent neutrophils, associated nuclear dust, and red blood cell extravasation); hematoxylin and eosin stain (magnification x 200).



Possible Drugs Associated with Leukocytoclastic Vasculitis^{a,1-4}

Antimicrobials (chloramphenicol, clindamycin, gentamycin, isoniazid, macrolides, penicillin and beta-lactams, quinolones, rifampicin, sulphonamides)
 Antivirals (eg, didanosine)
 Vaccines (anthrax, hepatitis A, hepatitis B, hepatitis C, influenza, rubella, pneumococcal, smallpox)
 Interferons (alpha, beta, gamma)
 Antithyroid agents (carbamazepine, methamazole, propylthiouracil)
 Anticonvulsants (phenytoin, carbamazepine, valproic acid)
 Antiarrhythmics (amiodarone, procainamide, quinidine)
 Diuretics (chlorthalidone, furosemide, hydrochlorothiazole, spironolactone)
 Other cardiovascular agents (acebutolol, atenolol, captopril, diltiazem, guanethidine, hydralazine, methyl dopa, nifedipine)
 Anticoagulants/thrombolytics (heparin, streptokinase, warfarin)
 Antineoplastic drugs (allopurinol, azathioprine, busulphan, chlorambucil, colchicine, cyclophosphamide, leflunomide, levamisole, melphalan, methotrexate, retinoids, tamoxifen)
 "Biologic" immune modulatory agents (TNF antagonists, rituximab, omalizumab)
 Hematopoietic growth factors (G-CSF, GM-CSF)
 Aspirin
 Nonsteroidal antiinflammatories
 Psychotropic agents (amitriptyline, clozapine, diazepam, maprotiline, trazodone)
 Sympathomimetics (ephedrine, methamphetamine, methylenedioxymethamphetamine, phenylpropanolamine)
 Others (aromatase inhibitors, bromide, cimetidine, cocaine, chlorpropamide, cromolyn, dextran, diphenhydramine, D-penicillamine, gold, heroin, iodinated contrast media, metformin, phenacetin, potassium iodide, quinine, statins, sulfasalazine, terbutaline)

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G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; TNF = tumor necrosis factor.

^a Adapted with kind permission from Merkel PA. Drug-induced vasculitis. In: Hoffman GS, Weyand CM, Langford CA, Goronzy JJ, editors. *Inflammatory diseases of the blood vessels*. 2nd ed. Oxford, UK: Wiley-Blackwell; 2012. DOI: <https://doi.org/10.1002/9781118355244.ch34>. ©2012 Blackwell Publishing Ltd.

(see Sidebar: Possible Drugs Associated with Leukocytoclastic Vasculitis). Apart from medications, other conditions have been associated with LCV (see Sidebar: Factors Implicated in the Etiology of Leukocytoclastic Vasculitis). Most known causes can be excluded by this patient's medical history, examination, and serum investigations. Myasthenia gravis has been rarely associated with microscopic polyangiitis and polymyositis, but to the best of our knowledge, an association with LCV has not been previously reported.⁵ Furthermore, LCV has not previously been reported to be associated with pyridostigmine.

This patient was receiving warfarin, which has been previously implicated as a causative agent of LCV; however, he had been on a stable dose of warfarin for seven years, making it an unlikely culprit. A literature review⁶ revealed most cases of warfarin-induced LCV were associated with histologic findings of prominent fibrinoid necrosis, which were absent in our case. The rash also regressed in our patient without the cessation of warfarin, again suggesting it was unlikely to be the causative agent. The same argument can be made for the other drugs present in the patient's medication regimen, which had

not been altered in more than two years and were continued during the period during which the patient's rash regressed.

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 one to three weeks after drug initiation. Additionally, it is important for clinicians to be aware that drug-induced vasculitis can occur after increasing the dose of a medication or a rechallenge of the offending drug.^{7,8}

Differentiating drug-induced LCV from other causes on the basis of histology alone is difficult owing to the histologic variation of the disease. A study conducted in 2006 found a higher proportion of tissue eosinophilia histologically in those with drug-induced LCV.⁴ However, tissue eosinophilia was not present in all cases of drug-induced LCV. Additionally, tissue eosinophilia was observed in some cases of non-drug-induced LCV. This suggests that although tissue eosinophilia may be common, it is neither sensitive nor

specific for drug-induced vasculitis.⁴ In our case, prominent tissue eosinophilia was not noted.

It is difficult to conclusively prove a single drug as the causative agent for LCV without rechallenging with the same medication. We felt it would be unethical to give pyridostigmine to our patient because his ocular myasthenia gravis is currently in remission. The aim of this report is to make clinicians aware of the possible association, previously undescribed, between pyridostigmine and LCV. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

The authors wish to thank Reshma Shettigar, MD, for her kind and generous assistance in the preparation of this manuscript.

Mary Corrado, ELS, provided editorial assistance.

How to Cite this Article

Singh G, Hodgson T, Clarke DE. Leukocytoclastic vasculitis secondary to pyridostigmine (Mestinon): Report of a possible first case. *Perm J* 2017;21:15-240. DOI: <https://doi.org/10.7812/TPP/15-240>.

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Factors Implicated in the Etiology of Leukocytoclastic Vasculitis¹⁻⁴

Drugs and drug additives (see Sidebar: Possible Drugs Associated with Leukocytoclastic Vasculitis)
 Malignancy (eg, multiple myeloma)
 Infections (eg, hepatitis B, hepatitis C, tuberculosis, endocarditis, human immunodeficiency virus, parasitic infections)
 Connective tissue diseases (eg, mixed connective tissue disorder)
 Rheumatologic diseases (eg, systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, polymyositis, mixed connective tissue disorder)
 Gastroenterologic diseases (eg, Crohn disease, ulcerative colitis)
 Cryoglobulinemia
 Vaccines
 Insect bites
 Chemicals
 Toxins
 Foods
 Idiopathies

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