Cutaneous leukocytoclastic vasculitis associated with verapamil and atorvastatin: A case report

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Introduction

Vasculitis is an inflammatory disease with variable end-organ damage that is classified based on involvement of small, medium or large vessels.[1] Leukocytoclastic vasculitis is a small-vessel vasculitis predominantly affecting dermal capillaries and venules, and often secondary to underlying systemic vasculitis, infection or drug exposure.[1] Commonly implicated drugs include beta-lactam antibiotics and non-steroidal anti-inflammatory drugs,[1] while calcium channel blockers and hydroxymethylglutaryl-coA reductase inhibitors (statins) have been rarely associated[2-6] – with no previous formal case report for verapamil. We present a case of cutaneous leukocytoclastic vasculitis associated with recently initiated verapamil and atorvastatin.

Case Presentation

An 82 year-old woman presented to hospital with a two-day history of a bilateral lower limb purpuric rash starting over her distal calves with ascent to her thighs (Figure 1a–b). The rash was non-pruritic and mildly tender. She had no fevers, myalgia, arthralgia, oral or genital ulcers, respiratory or sinus symptoms, neurological symptoms, Raynaud's phenomenon or oesophageal dysmotility. She did not have a previously similar rash. She was otherwise well with no preceding infective symptoms. She did not have direct skin contact with allergenic materials.10 days prior to rash onset, she was commenced on verapamil 40 mg immediate-release tablet twice daily and atorvastatin 40 mg tablet nocte by her cardiologist for palpitations and dyslipidaemia. She took these medications as prescribed for 12 consecutive days until hospital presentation. She had never taken these medications previously.

Her medical history included Sjogren's syndrome diagnosed three years prior with high-titre centromere pattern anti-nuclear antibodies (ANA) and sicca symptoms – which were stable on long term hydroxychloroquine 200mg once daily treatment. She also had a left submandibular gland Mucosa-associated lymphoid tissue (MALT) lymphoma successfully excised one year prior and was since in remission without needing systemic therapy. Her long-term medications also included aspirin 100 mg once daily for primary prevention, and over-the-counter magnesium, fish oil and vitamin C supplements taken as per directions. She had no known allergies. Vaccinations were up to date including four SARS-CoV-2 vaccinations– receiving the last vaccine six months prior without any adverse effects. She had never smoked or taken any illicit drugs and had no alcohol consumption.

On examination, her observations were normal and she was afebrile. She had bilateral lower limb purpura from distal calves to proximal thighs. Over the course of the two-day admission, the purpura progressed with coalescing of lesions and ascending involvement of the trunk and upper limbs (Figure 1c–d). She did not have active tenosynovitis, deforming polyarthropathy or nail abnormalities. She had no stigmata of scleroderma or infective endocarditis. She had no ocular inflammation, spondyloarthropathy, aphthous ulcers, or other abnormal rashes. She had no proximal weakness or focal neurological deficits. Her cardiorespiratory examination was unremarkable and she was euvolaemic. Her abdominal examination was unremarkable with

no hepatosplenomegaly. She did not have significant lymphadenopathy in the cervical, axillary or inguinal regions.

Her chest x-ray was unremarkable with no consolidation, interstitial markings or cardiomegaly. Full blood count revealed a mild normocytic anaemia in keeping with anaemia of chronic disease, as well as a mild neutrophilia, lymphopenia and monocytosis in keeping with an activated immune response (Table 1). There was no eosinophilia. Platelet count and coagulation profile were normal. C-reactive protein and erythrocyte sedimentation rate were mildly elevated and high-normal respectively; mild hypoalbuminaemia and decreased transferrin saturation were present in keeping with an acute inflammatory state. Serum electrolytes, urea, creatinine, liver function tests and haematinics were unremarkable. Urine investigations revealed no detectable proteinuria, dysmorphic red cells or casts. Infectious serology was negative for hepatitis B, hepatitis C and human immunodeficiency virus (Table 1).

Autoimmune serology was significant for a high-titre centromere pattern ANA, with negative extractable nuclear antigen antibody screen (ENA). Type II cryoglobulin was detected with a polyclonal and monoclonal immunoglobulin M (IgM) component (Table 1). Correspondingly, rheumatoid factor (RF) was elevated and there was marked C4 hypocomplementaemia. Cryoglobulin status was unknown prior to presentation. Anti-double stranded deoxyribonucleic acid (Anti-dsDNA), anti-cyclic citrullinated peptide (Anti-CCP) and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Serum immunoglobulin G (IgG), A (IgA) and IgM were within normal range. Serum protein electrophoresis was unremarkable with no paraprotein (Table 1).

Histopathology of the purpuric rash revealed leukocytoclastic vasculitis involving small vessels in the papillary and upper reticular dermis, with endothelial swelling and associated perivascular infiltrate of neutrophils, lymphocytes, few eosinophils, and leukocytoclasis (Figure 2a). Direct immunofluorescence revealed positive staining of the vessel walls for IgM (Figure 2b), C1q and C3 (Figure 2c). Staining for IgG and IgA (Figure 2d) was negative.

Based on the presentation and results, a diagnosis was made of mixed cryoglobulinaemia secondary to Sjogren's syndrome, with new onset cutaneous leukocytoclastic vasculitis arising from a differential diagnosis of a drug-induced type III hypersensitivity reaction and/or flare of cryoglobulinaemic vasculitis.

Outcome and Follow-up

Atorvastatin and verapamil were ceased from hospital presentation. Prednisolone 30 mg once daily was commenced and she was discharged with a plan to reduce dosage by 5 mg every five days. Upon follow-up one week later, there was marked improvement of the purpuric rash with no residual scarring or pigmentation. On one month follow-up, the rash had resolved and there was no evidence of end-organ or systemic vasculitis manifestations.

Discussion

Calcium channel blockers and statins have been rarely associated with leukocytoclastic vasculitis, with only a few case reports in the literature.[2-6] Of calcium channel blockers, only diltiazem,[3] lercarnidipine,[4] and amlodipine[5] have been implicated. We present a case of leukocytoclastic vasculitis associated with atorvastatin and verapamil. Using the Naranjo scale,[7] this case scored five points, making it a probable association. To the best of our knowledge, this represents the first formal report of leukocytoclastic vasculitis associated with verapamil, and only the second report associated with atorvastatin.[2]

Given both medications were started and ceased simultaneously, it is unclear whether the inciting agent was verapamil, atorvastatin, or the combination. It is well recognised that verapamil and atorvastatin interact via CYP3A4 enzyme and P-glycoprotein inhibition.[8] In this case, use of this combination may have increased the concentration of either drug to supratherapeutic levels and therefore increased the risk of inducing leukocytoclastic vasculitis – assuming a dose-dependent mechanism.

We postulate that the leukocytoclastic vasculitis resulted from a type III hypersensitivity reaction – where

drug-induced aberrant antibody production leads to immune complex formation and deposition in small vessels causing vasculitis – thought to be the general mechanism in drug-induced leukocytoclastic vasculitis.[9] This is supported by positive IgM and complement staining on immunofluorescence, skin-limited disease, and rash onset within the typical window of seven to ten days after commencing medications.[1]

However, the patient also had typical features of mixed cryoglobulinaemic vasculitis – the purpuric rash with leukocytoclastic vasculitis, C4 hypocomplementaemia, elevated RF and type II cryoglobulinaemia with polyclonal and monoclonal IgM components – which would also account for positive IgM and C3 staining on immunofluorescence studies. Cryoglobulinaemia is most likely secondary to Sjogren's syndrome given the recognised association.[10] Given the temporal relationship between initiation of the medications and development of leukocytoclastic vasculitis, a second postulated mechanism is drug-induced augmentation of cryoglobulinaemia – leading to an immune complex-mediated flare of cryoglobulinaemic vasculitis.[10] To the best of our knowledge, this would be the first reported case of a cryoglobulinaemic vasculitis flare associated with atorvastatin and verapamil.

It is possible that both mechanisms contributed in this case. Given the vasculitis was skin-limited, we favour the former hypersensitivity reaction as the predominant mechanism over a drug-induced flare of cryoglobulinaemic vasculitis – as this typically exhibits joint, renal and neurological manifestations,[10] which were absent in this patient.

Future research into molecular mechanisms would be beneficial to better understand the properties of certain medications which mediate autoimmunity and clarify genetic susceptibility to drug-induced vasculitis.[9]

In summary, we present a case of biopsy-proven leukocytoclastic vasculitis associated with verapamil and atorvastatin. We postulate the mechanism to be a type III hypersensitivity reaction or a drug-induced flare of cryoglobulinaemic vasculitis secondary to Sjogren's syndrome. This case report highlights the need to carefully consider drug interactions and monitor for rare adverse effects after initiating the relatively commonly prescribed medications of atorvastatin and verapamil – particularly in patients with autoimmune disease.

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