

Herpes zoster reactivation presenting as unilateral small vessel vasculitis in a patient taking upadacitinib

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Varicella zoster virus (VZV) is a neurotropic human herpes virus belonging to the genus *alpha herpesviridae*. The virus is responsible for primary infection resulting in varicella/chickenpox and reactivation from latent infection causing herpes zoster (HZ) reactivation, also known as shingles, in the setting of diminished cell immunity. HZ reactivation occurs worldwide and has an age-dependent incidence, with risk being highest in the elderly. The diagnosis of HZ reactivation is made clinically based on its typical presentation of a vesicular exanthema in a cutaneous nerve distribution, and treatment initiated in the first 72 hours reduces acute symptoms.¹ HZ reactivation can have a range of clinical presentations, although cutaneous small vessel vasculitis is seldom reported, with only a handful of cases in the literature to date.

Case

A 76-year-old Māori woman presented to our emergency department (ED) for evaluation of a painful rash. She reported that 5 weeks prior she developed painful red papules on the right lower leg, which subsequently developed into ulcers in the week prior to presentation. She denied a history of vesicles or other systemic symptoms. Prior to presentation she had sought medical attention in Australia while on vacation and had been investigated with a lower limb ultrasound to assess for deep venous thrombosis, which she reported was normal, and had trialled a course of antibiotics to no effect. On initial assessment examination the right lower leg showed well-demarcated ulcers with sharp edges and shallow bases. The patient had no other examination features to suggest systemic vasculitis, and the lesions had not spread since they first appeared. The patient reported no changes in medications and no exposure to any

new topical agents or supplements.

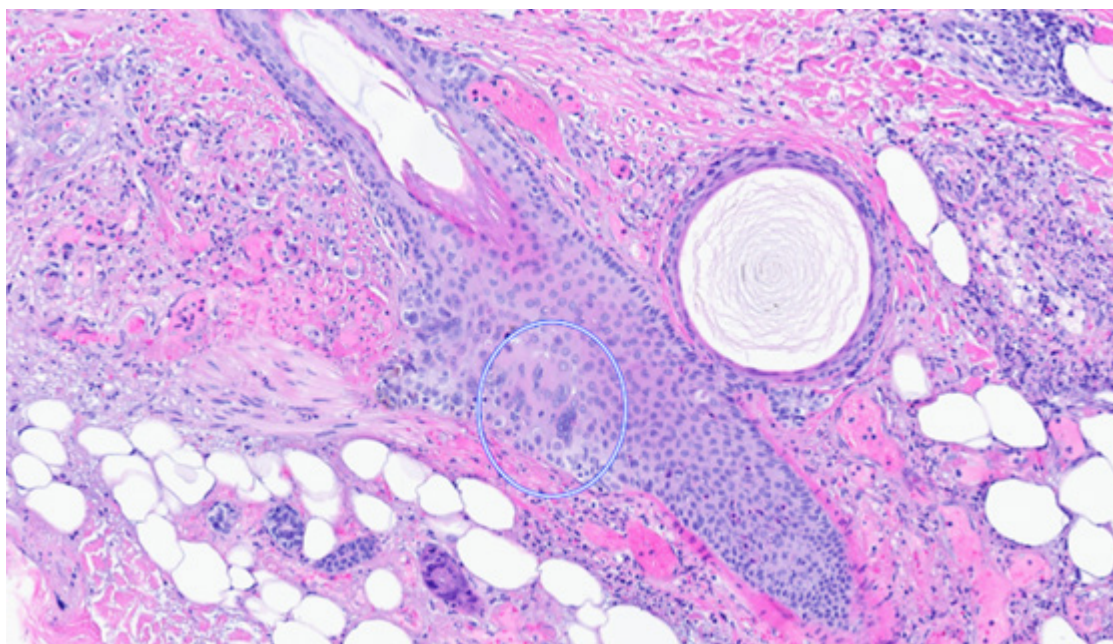
The patient had a background history of rheumatoid arthritis (RA) diagnosed in 1994, currently managed with methotrexate 20mg weekly and upadacitinib 15mg daily. Other medical conditions included ischaemic heart disease with prior coronary artery bypass grafting, type 2 diabetes, treated latent tuberculosis and hypertension. Her other medications included folic acid, cholecalciferol, aspirin, losartan, atorvastatin, amlodipine, doxazosin, metoprolol, furosemide, pregabalin and solifenacin.

Following admission to the hospital's general medicine service, wound care and analgesia were provided, and investigations to the underlying cause were initiated. A differential diagnosis was formulated, and this included embolic disorders, infective entities and autoimmune small vessel vasculitides. Routine blood tests showed a mild inflammatory picture and a long-standing normocytic anaemia. Chest radiograph and electrocardiogram showed no new abnormalities. Computed tomography (CT) imaging revealed only minimal aortic atheroma, and given the distribution of the lesions, an embolic process was not favoured as a diagnosis. Immunological tests for autoimmune causes of small vessel vasculitides were all non-contributory, including anti-neutrophil cytoplasmic antibody (ANCA), complement and cryoglobulin analysis. Infectious serologies including HIV, hepatitis B/C and typhus fever studies were also negative. As a result, a skin biopsy was performed on which mycology stains, tuberculosis (stains and DNA polymerase chain reaction) and histology were performed. Histology showed characteristic viral inclusions within keratinocytes and, as such, viral swabs of the lesions were collected, which confirmed VZV DNA and confirmed the final diagnosis of HZ reactivation presenting as unilateral cutaneous small vessel vasculitis.

Figure 1: Photograph of the patient's right lower limb demonstrating multiple ulcers consistent with small vessel vasculitis. Several smaller lesions that were consistent with palpable purpura are seen on the lower medial aspect. *Photo with consent from patient.*



Figure 2: Punch biopsy of skin demonstrating neutrophil fragmentation and fibrinoid necrosis of the blood vessel walls consistent with leukocytoclastic vasculitis. The encircled section demonstrates keratinocytes below a small vesicle with viral inclusions, in keeping with herpetic infection. Image used with permission from *Pathlab Tauranga*.



Summary

On the basis of histology results and viral swabs, a diagnosis of HZ reactivation presenting as cutaneous small vessel vasculitis was established. Intravenous acyclovir was initiated at 10mg/kg every 8 hours, and the lesions regressed over 2 weeks. The patient improved to discharge home. Before the patient's discharge it was considered whether to stop the patient's immunosuppression. Given the patient had failed therapy with all other available biologic and synthetic disease modifying anti-rheumatic drugs, it was decided in conjunction with the patient and her rheumatologist that it was necessary to continue her therapy with methotrexate and upadacitinib. Subsequently, a decision was made to advise the patient to seek vaccination for HZ reactivation with the adjuvanted subunit vaccine *Shingrix* to reduce future risk of HZ reactivation.

Discussion

Unilateral small vessel vasculitis as a presentation of HZ reactivation is rare, with only four cases reported in the literature, this being the first case in New Zealand and the second case internationally in a patient treated with upadacitinib.²⁻⁵

A key feature of this case was the absence of a classical vesicular phase, as seen in typical HZ reactivation. This feature was shared with the other cases described internationally.

Pertinent to this patient's risk of HZ reactivation is the use of immunosuppression. The risk of HZ reactivation with upadacitinib is dose dependent and is higher than both methotrexate alone or in combination with a tumour necrosis factor (TNF) inhibitor.⁶ Concomitant steroid use further increases the risk. Additionally, patients with RA have a twofold risk of HZ reactivation compared to the general population.⁶

Upadacitinib is a targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD) that preferentially inhibits Janus Kinase 1 (*JAK1*), which is involved in downstream signalling and inflammation resulting from cytokines of the γ c family, including IFN- γ . The adaptive immune response to intracellular pathogens such as viruses is primarily driven by T_H1 cells. T_H1 cells are reliant on *JAK1* signalling, as opposed to T_H2 cells and T_H17 cells, which are not. Hence, the inhibition of *JAK1* signalling leads to an increased risk of intracellular viral replication, potentially above that of other infectious aetiologies. Additionally,

CD8 cells, B cell differentiation and antibody production are dependent on *JAK1* signalling.⁷

Although the most common presentations of HZ reactivation are familiar to physicians, atypical presentations are possible and present a diagnostic challenge, as in this case. HZ reactivation has been associated with vasculopathy, particularly in immunocompromised patients. This can present with a myriad of central nervous system findings including encephalitis, meningoencephalitis, vasculitis, myelitis and Guillain-Barré syndrome.¹ Although the virus typically infects dorsal ganglion cells, it has been shown to infect vascular endothelial cells as part of a vasculopathy, which we propose was demonstrated to be the instance in this case. This vasculopathy with HZ reactivation also is linked to a higher risk of stroke.⁸

Treatment with acyclovir was effective in this case, highlighting the importance of antiviral therapy in preventing complications of HZ reactivation. However, preventing recurrence of HZ reactivation remains an issue. The European Alliance of Associations for Rheumatology (EULAR) recommends vaccination with a live attenuated vaccine to be considered in patients with autoimmune inflammatory rheumatic diseases; however, it must be administered 4 weeks prior to the initiation of tsDMARD or immunosuppressive therapy.⁹ For patients without a confirmed history of primary varicella infection, serological testing is essential to prevent primary varicella infection.

More recently, a novel inactivated subunit vaccine *Shingrix* has been available in New Zealand. Composed of VZV glycoprotein E and an adjuvant, this vaccine has evidence for the prevention of HZ reactivation and has been shown to be superior to the live attenuated vaccine.^{9,10} It has been shown to be immunogenic in immunocompromised patients, including those established on immune suppressing medications, and is recommended for use in patients aged 18 and over with autoimmune inflammatory rheumatic conditions by the American College of Rheumatology.¹⁰⁻¹³ Furthermore, the US Advisory Committee on Immunization Practices recommends the vaccine as safe and effective in immunocompromised patients.¹³

The continued use of tsDMARDs after HZ reactivation must be an individualised decision, given the further risk of HZ reactivation. Our patient had previously had ineffective RA control with all other available treatments for RA in New Zealand, and as such upadacitinib was continued

and the patient was advised vaccination with the *Shingrix* vaccine. We considered the further option of continuous valacyclovir prophylaxis in our patient if further events were to occur.

In conclusion, this case demonstrates a rare presentation of HZ reactivation, which serves as

a reminder of the possible presentations of HZ reactivation, and a differential for a unilateral vasculitis in patients on tsDMARDs, as well as the importance of advocacy for vaccination in such patients.

COMPETING INTERESTS

Nil.

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