Two cases of atypical herpes zoster in people taking oral Janus kinase inhibitors

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Patient A

A 35-year-old woman presented to her dentist following 3 days of pain localized to her right mandible, with associated edema of the right cheek and skin changes to the right pre-auricular region and buccal mucosa. She had been on oral upadacitinib, a Janus kinase (JAK) inhibitor, 30 mg once daily for treatment of atopic dermatitis for 17 months before the onset of pain. A source of the pain could not be identified on an in-office radiograph, so she was urgently referred to an oral maxillofacial surgeon and seen the following day. The surgeon noted a 1 cm, friable, rolled-edge ulcer on the right pre-auricular site and unilateral lymphadenopathy (Figure 1). Clinical concern for skin cancer prompted urgent referral of the patient to dermatology, with a prescription for oral cephalexin 500 mg 4 times daily for possible cellulitis.

We saw the patient in our dermatology clinic the following day. We took viral and bacterial wound swabs and performed a skin biopsy. We prescribed oral amoxicillin (875 mg) and clavulanate (125 mg) twice daily for 10 days, and oral valacyclovir 1 g 3 times daily for 10 days as empiric treatment for possible cellulitis and herpes zoster, respectively. We also ordered an urgent soft-tissue ultrasound of the right cheek to exclude an associated abscess.

Culture of samples from the patient's viral and bacterial wound swabs yielded varicella zoster virus (VZV) and *Staphylococcus aureus*, respectively. The ultrasound was unremarkable. Microscopy of the skin biopsy showed an ulceration with prominent superficial cutaneous necrosis, abundant superficial bacterial colonies, and features consistent with herpes viral cytopathic effect. On day 5 of valacyclovir, the patient developed headache, neck stiffness, and widespread erosions on the chest and torso.

Given our concerns for disseminated VZV and possible meningitis, we advised that the patient visit the emergency department. On examination there, she had normal vital signs, a normal hemoglobin level, and a lymphocyte count of 2.2 (normal range 0.5–4.5) × 10^9/L, with slightly elevated eosinophils of 0.8 (normal range 0.0–0.7) × 10^9/L. Her C-reactive protein level was mildly elevated at 15 (normal < 8.0) mg/L, along with normal creatinine and alanine aminotransferase, alkaline phosphatase and aspartate aminotransferase levels. The emergency physician performed a lumbar puncture, and cerebrospinal fluid (CSF) samples were sent for herpes simplex virus and VZV nucleic acid testing (NAT).

Key points

- Janus kinase (JAK) inhibitors are a class of immunosuppressive medications increasingly used to treat various inflammatory and autoimmune disorders and cancer.
- Immunosuppressive medications may increase the risk for varicella zoster virus (VZV) reactivation, and JAK inhibitors such as upadacitinib are known to be associated with increased risk.
- Clinicians should be alert for unconventional morphologic presentations of herpes zoster in patients taking JAK inhibitors.
- Taking wound swabs for bacterial and viral culture is advisable; VZV polymerase chain reaction is the gold standard test for diagnosis of VZV infection.

The patient was admitted to hospital for intravenous (IV) acyclovir for 5 days, then transitioned to oral valacyclovir 1000 mg 3 times daily for 21 days. On day 2 of admission, the NAT identified VZV DNA in her CSF. She did not have other complications of disseminated VZV, and on day 6 was discharged from hospital. The patient had not previously had vaccination against VZV, but received her first vaccination in hospital, when all the vesicles had crusted over. We followed up 1 week after discharge. In consultation with an infectious diseases specialist, we restarted the patient on upadacitinib 30 mg once daily, 4 weeks after she received her first vaccination dose. The infectious disease specialist also recommended valacyclovir 500 mg once daily for VZV prophylaxis going forward while the patient was on upadacitinib.

Patient B

An 80-year-old woman presented to our dermatology clinic with multiple punched-out ulcers on the right forearm, right upper arm, and upper back (Figure 2). Before the onset of these lesions, she was taking oral upadacitinib 30 mg once daily for 3 months, for the treatment of presumed hypereosinophilic syndrome, given her history of dermatitis and hypereosinophilia without other cause. Although clinically her eruption was more suspicious for ecthyma or a deep fungal infection, viral and bacterial swabs were performed, and cultures yielded VZV and *S. aureus*, respectively. Microscopic examination of a punch biopsy showed impetiginized ulceration with mixed inflammatory infiltrate, which was predominantly neutrophilic, as well as a superficial

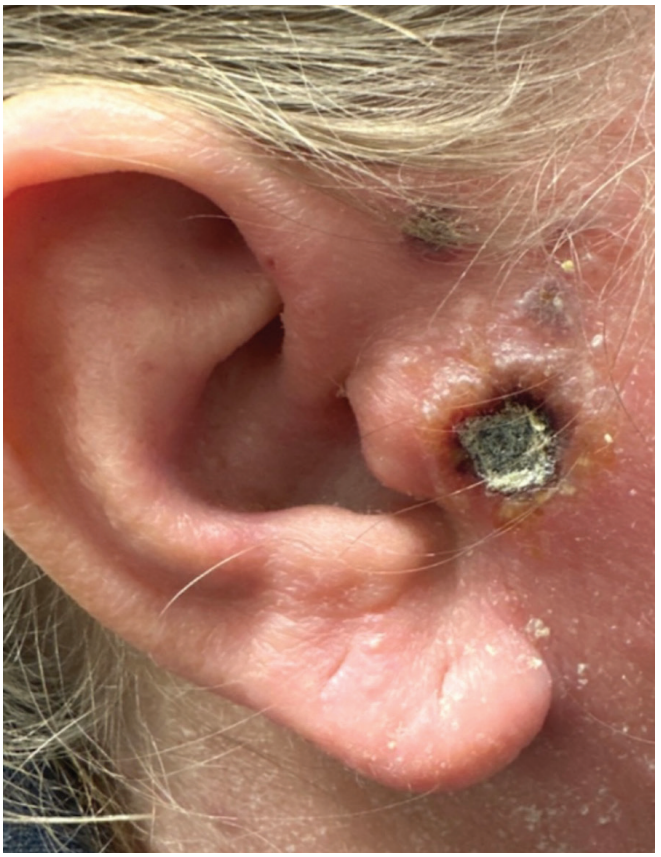

Figure 1: A 1-cm ulcer with a necrotic base and rolled borders in the right pre-auricular region in of a 35-year-old woman with herpes zoster.

perivascular lymphocytic infiltrate with occasional eosinophils. A complete blood count showed a hemoglobin level of 108 (normal range 120–160) g/L and lymphocyte count of 2.1 (normal range 0.5–4.5) × 10^9/L, with a slightly elevated eosinophil level of 0.9 (normal range 0.0–0.7) × 10^9/L. The patient had previously been immunized against VZV, with the first dose at 2 years before the eruption and the second dose 1 year previously. Upadacitinib was discontinued and she was given oral valacyclovir 1 g 3 times daily for 10 days. She has subsequently made a full recovery and was not restarted on upadacitinib.

Discussion

Reactivation of VZV, known as herpes zoster, typically presents as a painful eruption of vesicles and erythematous papules or pustules in a dermatomal pattern. Although about 30% of people will be affected by herpes zoster in their lifetime,[1] patients treated with immunosuppressant medications are at an increased risk of VZV reactivation and complications.[2] Among immunosuppressant medications, JAK inhibitors are a therapeutic class increasingly used to treat a multitude of inflammatory, autoimmune, and cancerous conditions. It is likely that both generalists and specialists will require expertise in managing their adverse effects. Although patients taking these agents have shown promising treatment responses for conditions such as inflammatory bowel disease, rheumatoid arthritis, and atopic dermatitis, JAK inhibitors have been shown to increase the risk of VZV reactivation.[3,4]

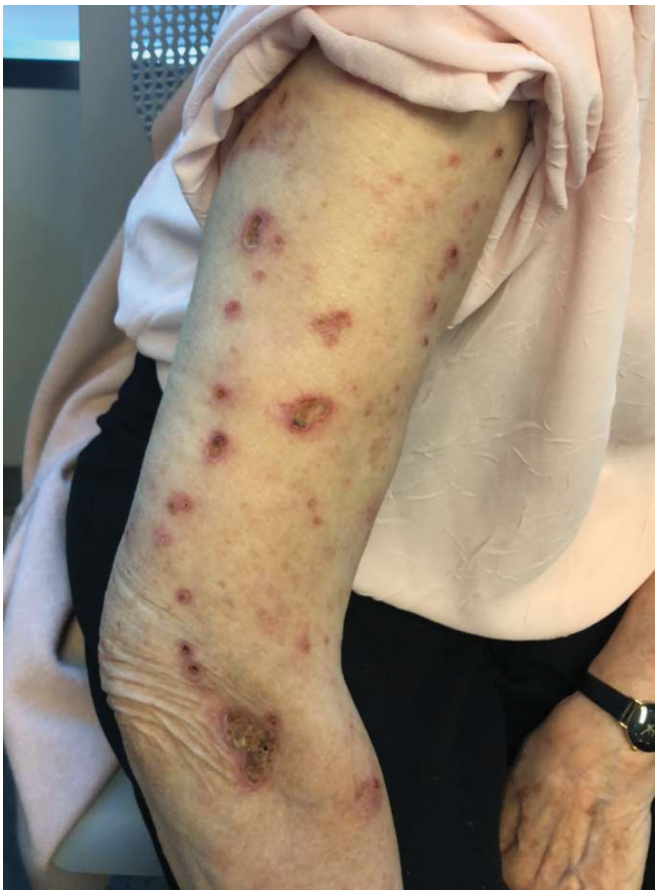

Figure 2: Numerous punched-out ulcers with a necrotic base and erythematous rim on the right forearm and right upper arm of an 80-year-old woman with herpes zoster.

We described 2 unusual presentations of herpes zoster, confirmed with both tissue histology and viral polymerase chain reaction (PCR), the gold standard for diagnosis of VZV infection, in patients treated with oral upadacitinib, a JAK inhibitor, which highlight possible atypical presentations of VZV in people who take JAK inhibitors. Upadacitinib is a JAK inhibitor with high selectivity for JAK1. It is currently approved by Health Canada for moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, moderate to severe atopic dermatitis, Crohn disease, and ulcerative colitis. It is effective in inhibiting cytokines responsible for inciting the above inflammatory conditions, and also thought to lower host immune defence against pathogenic bacteria, fungi, and viruses via inhibition of interferon γ.[5] Specifically, interferon γ strongly suppresses VZV replication; thus, when blocked by JAK inhibitors, it increases the risk of reactivation.[5]

In a 2022 phase 3 trial with use in rheumatoid arthritis, Winthrop and colleagues reviewed 5306 patients, of whom 3209 received upadacitinib 15 mg once daily and 1204 received upadacitinib 30 mg once daily.[3] Herpes zoster events were found to occur in 12.5% of the upadacitinib 30 mg once daily group and 6.4% in the upadacitinib 15 mg once daily group.[3] Disseminated herpes zoster occurred in 5.9% of patients taking upadacitinib 15 mg and 7.3% of patients taking upadacitinib 30 mg.[3] Morphologic descriptions of these eruptions were not provided, but the increased risk of VZV reactivation is well documented.

Diagnosis and management

The unusual presentations of herpes zoster in patients taking oral JAK inhibitors can pose challenges for diagnosis. Previously reported cutaneous atypical herpes zoster presentations include herpes sine herpete (lack of a cutaneous eruption, but associated pain) and bilateral herpes zoster.[6] In patients who are immunocompromised in other settings — such as postorgan transplant and chemotherapy — atypical presentations of scattered ulcerations in more than 3 different dermatomes[7] and multiple converging and crusted papules and vesicles spreading cephalocaudal mimicking a drug eruption[8] have been reported, respectively.

Risk factors previously identified to increase the risk of herpes zoster for patients receiving upadacitinib include a history of herpes zoster and Asian geographic origin.[3]

If a patient develops herpes zoster, the product monograph recommends temporarily interrupting treatment until the episode resolves. The decision to start intravenous versus oral antivirals will depend on the patient's clinical status.

Although the benefit of herpes zoster vaccination may vary depending on the immunosuppressive agent, it is generally advisable before initiation of JAK inhibitors.[4] Shingles vaccination is a 2-part, nonlive, recombinant zoster vaccine. It is approved for prevention of herpes zoster in adults aged 50 years or older, and adults aged 18 years or older who are immunocompromised owing to disease or treatment. The original clinical trials using shingles vaccination in immunocompetent people had an overall vaccine efficacy of 97.2%.[9] The United States Advisory Committee on Immunization Practices estimates that the vaccine efficacy in immunocompromised people ranges between 68.2% (autologous hematopoietic stem cell transplant recipients) and 90.5% (immune-mediated diseases).[10] The vaccine's low rate of adverse effects and potentially large benefit supports immunization in the immunocompromised patient population.[10]

The numerous necrotic ulcers extending to an entire limb and back, and the deep pre-auricular ulcer seen in our cases are not conventional herpes zoster presentations; these features serve to highlight that herpes zoster in patients taking oral JAK inhibitors may present with unusual morphologies. If not appropriately diagnosed and treated in a timely manner, patients may develop disseminated infections with possible visceral involvement and even death.

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The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features, or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.