

Disseminated Varicella Zoster Virus Infection with Encephalitis in a UC Patient Receiving Infliximab

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Opportunistic infections occur at an increased rate in patients with inflammatory bowel disease (IBD), largely due to the use of immunosuppressants. One study found that the odds ratio for opportunistic infections in immunosuppressed patients compared to nonimmunosuppressed patients was 2.6 for patients on 1 drug and increased to 12.9 when 2 or more drugs were used.¹ Varicella zoster virus (VZV) is the causative agent of chickenpox and herpes zoster, and case studies have reported disseminated infections caused by VZV in patients on tumor necrosis factor α (TNF α) inhibitors.²⁻⁴ Although the incidence of infection can be decreased through vaccination, the VZV vaccine utilizes a live attenuated virus and is contraindicated in patients who are immunosuppressed.⁵ This report presents a case of disseminated VZV infection with encephalitis in an unvaccinated patient with ulcerative colitis (UC) who was receiving infliximab (Remicade, Janssen Biotech).

Case Report

A 71-year-old man with long-standing UC who had been maintained for years on infliximab presented to the emergency department with altered mental status, gait instability, and progressive weakness over several days. His last infliximab infusion had been 2 weeks prior to presentation. The patient's vital signs were notable for a temperature of 38.6°C and tachycardia. His physical examination revealed a vesicular rash with erythematous bases, including some hemorrhagic vesicles, that affected multiple dermatomes on the right upper extremity and

left chest (Figures 1 and 2). His mental status waxed and waned during the initial evaluation. His neurologic examination was nonfocal, and meningeal signs were negative. Blood and urine samples were cultured, and the patient was started on broad-spectrum antibiotics and acyclovir prior to neuroimaging and lumbar puncture.

Magnetic resonance imaging showed chronic small vessel disease that was unchanged from a previous examination in 2008. An analysis of the patient's cerebrospinal fluid (CSF) was significant for a nucleated cell count of 140 cells/ μ L (90% lymphocytes), a protein level of 125 mg/dL, and a glucose level of 106 mg/dL (plasma glucose level of 191 mg/dL). The patient's chemistries, liver function test results, and complete blood cell count were otherwise unremarkable. CSF culture and Gram staining; herpes simplex virus 1 and 2, cytomegalovirus, and Epstein-Barr virus titers; and cryptococcal antigen testing were all negative. VZV DNA was detected by polymerase chain reaction in the CSF, and the patient was diagnosed with disseminated VZV infection, including encephalitis. Although the patient remembered having varicella in childhood, the current presentation was the patient's first episode of shingles, and he denied receiving a VZV vaccination prior to initiation of infliximab therapy. The patient's mentation improved over several days, and he was discharged home to complete a 3-week course of intravenous acyclovir therapy. After completion of this therapy, his only residual symptom was postherpetic neuralgia.

Discussion

VZV is a member of the human herpesvirus family and is designated HHV-3. VZV infection initially presents as varicella (chickenpox), often during childhood. The virus usually remains dormant in cranial nerve and dorsal root

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Figure 1. A vesicular rash on an erythematous base consistent with herpes zoster involving areas of the left side of the patient's chest wall.

ganglia.² The virus may reactivate as herpes zoster (shingles), often in older or immunocompromised individuals. When the infection is limited, herpes zoster affects 1 or a few adjacent dermatomes, presenting as a painful vesicular rash that may be complicated by postherpetic neuralgia.²

VZV infection of the central nervous system (CNS) can present along a spectrum of meningoencephalitis. Meningitis is the infection and inflammation of the meninges, and this condition is classically seen in HIV-infected hosts.⁶ Encephalitis is the result of a VZV CNS vasculitis, which causes 1 of 3 morphologic syndromes based on the location of the vasculitis. When large cerebral vessels are affected, the result is an acute infarct manifesting as a focal neurologic deficit consistent with stroke.⁶ Large vessel disease is more common in immunocompetent hosts. Conversely, small vessel disease is almost always seen in immunocompromised individuals.⁷ Small vessel disease presents as the subacute onset of symptoms such as headache, fever, nausea, seizures, and mental status changes, with findings of aphasia, hemiplegia, and visual field deficits.⁷ The third and least common presentation of VZV encephalitis is due to infection of periventricular ependymal cells; this type of disease presents with gait disorder and hydrocephalus.⁶

The risk of herpes zoster is increased in patients with rheumatoid arthritis who are receiving TNF α inhibitors.⁸ In addition, the presentation of herpes zoster is usually more severe in these patients, and they have an increased risk of hospitalization.⁹ In the RATIO study, 24 cases of herpes zoster were reported in patients receiving TNF α inhibitors, and 8 of these cases were classified as severe (4 multidermatomal infections, 3 ophthalmic infections, and 1 case of meningitis).⁴

Two cases of VZV encephalitis have been reported in patients receiving TNF α inhibitors. The first case



Figure 2. A herpes zoster rash with some hemorrhagic vesicles involving multiple dermatomes in the right upper extremity.

occurred in a patient with psoriatic arthritis who was receiving adalimumab (Humira, Abbott).¹⁰ The patient received a 3-week course of acyclovir and had no residual symptoms. The second patient had rheumatoid arthritis and was receiving a combination of adalimumab and methotrexate.¹¹ This patient recovered but had persistent bilateral lower extremity weakness.

A live attenuated vaccine for herpes zoster is currently available and can decrease the rate of herpes zoster and the severity of postherpetic neuralgia.¹² In 2008, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination of nonimmunosuppressed adults above the age of 60 years.⁵ The safety and efficacy of the herpes zoster vaccine in patients receiving TNF α inhibitors is unknown. Previously published case studies have reported immunocompromised patients (patients with hematologic malignancies, patients receiving corticosteroids or chemotherapy, and transplant recipients) who developed disseminated disease following vaccination.^{13,14} A recent retrospective study identified 47 patients with rheumatoid arthritis or IBD who received the herpes zoster vaccine while receiving TNF α inhibitors. None of the 47 subjects developed herpes zoster in the 30 days after vaccination; however, the depressed immune system in these patients may not allow for generation of a protective immune response.¹⁵ Patients who are receiving immunosuppressive therapy have been shown to mount a diminished response to influenza and pneumococcal vaccines.¹⁶ The ACIP recommends that the herpes zoster vaccine be avoided in patients receiving TNF α inhibitors and that vaccination be deferred for at least 1 month after discontinuation of such therapy.⁵ Administering this vaccine prior to initiation of immunosuppressive therapy is ideal, and patients should wait 1–3 months after vaccination before starting TNF α inhibitors.¹⁷

Data indicate that IBD patients are underimmunized. Melmed and colleagues reported that only 9% of surveyed

IBD patients were vaccinated against pneumococcus, 28% against influenza, and 45% against tetanus.¹⁸ No data exist on rates of vaccination against VZV in this population. According to a recent study, only 14% of gastroenterologists inquired about vaccination history.¹⁹

The current case highlights the risk of the severe, potentially disabling infections that can occur when clinicians fail to vaccinate patients prior to initiating chronic immunosuppressive therapy. Although primary care providers coordinate patient care among specialists, immunosuppressive medications are often initiated by gastroenterologists or rheumatologists, and these specialists share the responsibility for assessing patients' vaccination status and providing patients with the appropriate vaccines. Protecting patients prior to initiating immunosuppressive therapy will help to ensure that the cure is not worse than the disease.

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Review

Varicella Zoster Virus Infection in Patients with Inflammatory Bowel Disease

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Varicella zoster virus (VZV) may cause either varicella (chickenpox) or herpes zoster (shingles). When VZV is contracted in childhood, the infection causes chickenpox and is characterized by a diffuse vesicular rash. Later in life, the virus may reactivate as herpes zoster, which typically causes a skin rash localized to a single dermatome. This infection may be followed by postherpetic neuralgia in 10–20% of cases. In an immunocompromised host, primary and reactivated VZV infection may cause disseminated disease—including hepatitis, pneumonia, and/or encephalitis—as described in our recent case report.¹ Corticosteroids, thiopurines, and anti-tumor necrosis factor (anti-TNF) agents are all associated with an increased risk of infection. The combination of any of these immunomodulatory agents further increases the risk of VZV reactivation.¹

The case reported by Elwir and associates highlights the importance of identifying patients who may require immunosuppressive therapy and considering appropriate

vaccinations prior to initiating such therapy.² Physicians should therefore query patients with inflammatory bowel disease (IBD) regarding their vaccination history and VZV exposure at the initial visit. VZV titers should be obtained prior to starting immunosuppressive therapy if prior exposure is uncertain. As the case by Elwir and colleagues demonstrates, however, although a patient may recall having chickenpox in childhood, history alone may not be adequate to assess for seropositivity.² In 1 study of 104 patients who remembered being exposed to VZV, 7 patients had negative or indeterminate VZV immunoglobulin (Ig) G titers. Of the 17 patients who reported a negative history of chickenpox, all had positive VZV IgG titers.³ If patients have no prior history of VZV or a negative serology result and immunosuppressive therapy is not imminent, they should be vaccinated against VZV. Additionally, nonimmunosuppressed patients aged 50 years or older should be given the zoster vaccine, which has been shown to decrease the incidence of herpes zoster by 51.3% and the incidence of postherpetic neuralgia by 66.5%.⁴ Unfortunately, a study by Melmed and colleagues showed that 11% of IBD patients did not reliably recall a history of chickenpox or varicella vaccination, and 75% of seronegative patients were receiving immunosuppressive therapy.⁵

Once patients are already immunosuppressed, the appropriateness of live vaccines is less clear. The concern is that the administration of live vaccines to immunosuppressed individuals may be associated with an increased risk of disseminated infection. Some doctors recommend that varicella vaccination be administered at least 1–3 months prior to initiating immunosuppressive therapy, but this recommendation is not based on a strong level of evidence.^{6,7} European guidelines state that the varicella vaccine may be administered up to 3 weeks prior to initiating immunomodulators.⁷ Additionally, recommendations state that the vaccine should not be given for at least 3 months following immunosuppressive therapy.⁷ While there are no clear guidelines regarding the timing of herpes zoster vaccination, a similar schedule can be considered. Although most physicians avoid live vaccination in immunosuppressed patients, the Advisory Committee on Immunization Practices advises that zoster vaccination may be considered in patients receiving short-term corticosteroid therapy (<14 days) or low doses of methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6-mercaptopurine (<1.5 mg/kg/day).⁶

A recent retrospective cohort study evaluated patients with immune-mediated diseases (including IBD) who had received herpes zoster vaccination.⁸ Six hundred and thirty-three of these patients were receiving biologic agents at the time of vaccination, including 551 patients who were receiving anti-TNF therapy. None

of the patients developed varicella or herpes zoster within 42 days of vaccination. Importantly, vaccination decreased the overall rates of herpes zoster in all patients, including those receiving biologic agents and steroids.

In addition to the potential risk of disseminated infection from live vaccines, some evidence suggests that vaccines may be less effective in patients who are immunosuppressed. However, this conclusion is also controversial. Children with IBD who were on immunosuppressive therapy and received the varicella vaccine were found to tolerate the vaccine well and to achieve appropriate seroconversion.⁹ A study of adult IBD patients receiving thiopurines found that they were able to generate a normal immune response to pneumococcal, tetanus, and *Haemophilus influenzae* type b vaccines.¹⁰ However, another study of IBD patients found that individuals receiving corticosteroids, biologic agents, and/or immunomodulators had a lower seroprotection rate following H1N1 influenza vaccination.¹¹ Seroprotection decreased with combination immunosuppressive therapy compared to monotherapy. Despite these data, vaccinating immunosuppressed patients with non-live vaccines in the hope of preventing infections is still reasonable and recommended.⁶

Once an IBD patient develops VZV infection, guidelines are unclear on the management of either primary varicella or reactivation of prior infection. While reactivation of VZV may be severe and can require hospitalization and/or cessation of immunosuppression, primary varicella infection is of particular concern due to the risk of significant morbidity and mortality.^{12,13} For an immunosuppressed IBD patient with either primary varicella or herpes zoster who appears to be well, treatment may consist of oral antiviral medication.¹ In more severe disease, intravenous antiviral therapy should be initiated, and an infectious disease consultation is recommended. Based on available (albeit limited) data, we would favor withdrawing immunosuppressive therapy in cases of primary varicella, although continuing immunosuppressive therapy in conjunction with antiviral therapy could be considered in cases of uncomplicated herpes zoster. If immunosuppressive therapy is withdrawn, clinicians can consider restarting this therapy once the patient's vesicles have resolved. However, reinitiation of immunosuppressive therapy should probably be done in consultation with an infectious disease specialist.

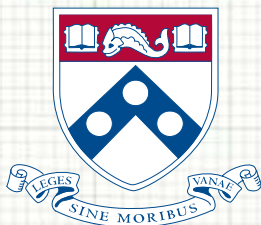
In summary, patients who are diagnosed with IBD should be queried about their history of VZV exposure at their initial visit. Patients who cannot recall a history of chickenpox in childhood should have their VZV IgG titers checked, and they should be advised to undergo vaccination if they are seronegative, provided that immunosuppressive therapy is not imminent. Providers

should also be aware that, while vaccinations may not be as effective in immunosuppressed individuals, they are nonetheless recommended. Treatment of VZV infection and management of the underlying immunosuppressive therapy varies depending on the severity of the disease and whether the infection is a primary infection or reactivation (shingles). Consultation with an infectious disease specialist is recommended.

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