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Case Report

When Immunity Falls Short: Meningoencephalitis Despite Vaccination - A Case Report

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Abstract

Varicella-zoster virus (VZV) significantly impacts the central and peripheral nervous systems, particularly in immunocompromised individuals. This case report details a rare presentation of VZV meningoencephalitis in a 42-year-old woman with interstitial lung disease and connective tissue disease undergoing lung transplant evaluation who presented with a thunderclap headache and a new-onset seizure. Despite normal initial MRI findings, further investigation with PCR of the cerebrospinal fluid (CSF) revealed the presence of VZV, indicating VZV meningoencephalitis. The patient had been immunosuppressed with prednisone, sulfasalazine, hydroxychloroquine, and mycophenolate and had received a 2 dose series of recombinant zoster vaccine (Glaxosmithkline, Brentford, England, UK) seven months prior to presentation. Initial diagnostic considerations included reversible cerebral vasoconstriction syndrome, but a lack of response to nimodipine and abnormal CSF findings shifted the diagnosis towards VZV meningoencephalitis. The patient was treated with intravenous acyclovir, which led to initial improvement. However, she developed bilateral lower extremity weakness after discharge, with MRI showing multifocal nodular leptomeningeal enhancement.

Subsequent tests ruled out coccidioidomycosis and suggested ongoing VZV infection. After extensive antiviral treatment with valaciclovir, the patient's condition stabilized, and she ultimately successfully underwent a lung transplant without complications. This case of VZV meningoencephalitis underscores the need for heightened clinical suspicion, vigilance, and prompt intervention in high-risk populations to prevent severe outcomes.

keywords
Shingrix vaccine; varicella-zoster virus; immunocompromised; lung transplant; meningoencephalitis

1. Introduction

Varicella-zoster virus (VZV) is associated with significant morbidity and mortality, with diverse manifestations [1]. Primary infection usually causes chickenpox (varicella), after which the virus becomes latent within nerve ganglia and can reactivate, causing herpes zoster (i.e., shingles). Herpes zoster (HZ) can have a variety of manifestations. In immunocompetent individuals, reactivation typically results in a vesicular rash confined to a single dermatome. However, in immunocompromised patients or more severe cases, VZV reactivation can lead to disseminated disease with systemic involvement, including neurologic complications such as meningitis and myelitis [2]. In immunocompromised individuals these complications often present atypically, necessitating a high degree of clinical suspicion for prompt diagnosis and treatment.

Complications from varicella infections significantly affect morbidity and mortality, especially among immunocompromised individuals. Vaccination remains the cornerstone of preventing VZV. Recombinant zoster vaccine (RZV) were introduced in 2017 as a safe and effective method to prevent reactivation of VZV in immunocompromised individuals [3-5]. We present a rare case of VZV meningoencephalitis in an immunocompromised patient despite RZV vaccination. This case highlights the importance of maintaining high clinical suspicion, vigilance, and prompt intervention in similar high-risk populations to prevent severe outcomes.

2. Case Presentation

2.1 Patient Information

A 42-year-old woman with a complex medical history, including interstitial lung disease and myositis associated with connective tissue disease, was undergoing evaluation for lung transplantation. She was chronically immunosuppressed, receiving a regimen that included prednisone, sulfasalazine, hydroxychloroquine, and mycophenolate mofetil.

2.2 Presenting Complaints

The patient presented to the emergency department with a thunderclap headache that fluctuated in intensity and was accompanied by worsening shortness of breath. During her evaluation, she experienced a new-onset tonic-clonic seizure lasting approximately 3-4 minutes,

characterized by right hand and gaze deviation and urinary incontinence. Notably, the patient had no prior history of headaches or seizures.

2.3 Medical History

- Immunosuppressive therapy: The patient was on prednisone, sulfasalazine, hydroxychloroquine, and mycophenolate mofetil.
- Vaccination history: She was seronegative for varicella zoster IgG but reported a history of childhood chickenpox. She received her second dose of the RZV, rather than Varivax due to high level of immunosuppression and childhood history of chickenpox, seven months prior to presentation.

2.4 Diagnostic Workup

1. Imaging studies:
   - MRI of the brain: Initially showed no acute intracranial processes.
   - Magnetic resonance angiography: Revealed beading in the distal left M1 and proximal right M2 segments but no significant luminal narrowing, raising concerns for reversible cerebral vasoconstriction syndrome, cerebral vasculitis, or fibromuscular dysplasia.
   - Cerebral angiogram: No evidence of cerebral vasculitis, but a small right posterior communicating artery infundibulum was identified.
2. Infectious disease consultation:
   - Given her immunocompromised state, viral meningoencephalitis, particularly due to VZV, became a leading concern after initial considerations of reversible cerebral vasoconstriction syndrome were ruled out due to lack of response to nimodipine.
3. Lumbar puncture:
   - Cerebrospinal fluid (CSF) analysis showed an elevated protein level and an abnormal white blood cell count with lymphocytic pleocytosis, consistent with a viral etiology.
   - PCR of the CSF revealed the presence of VZV, indicating VZV meningoencephalitis.

2.5 Treatment and Clinical Course

The patient was started on a course of intravenous acyclovir (14-day course in accordance with infectious disease consultation recommendations and Infectious Diseases Society of America (IDSA) guidelines [6]) alongside symptomatic management for her headache. Due to her viral infection, her dose of mycophenolate mofetil was reduced, and hydroxychloroquine was temporarily halted. Empiric antibiotics were maintained until cultures were finalized.

Upon completion of the intravenous antiviral treatment, the patient was discharged home but later returned to the emergency department with increasing bilateral lower extremity weakness, leading to an inability to ambulate.

2.6 Subsequent Investigations

- Follow-up lumbar spine MRI: Revealed multifocal nodular leptomeningeal enhancement involving the cauda equina nerve roots.
- Repeat lumbar puncture: Showed persistently elevated protein, lymphocytic pleocytosis, oligoclonal bands, and increased immunoglobulin synthesis rate, suggesting ongoing viral infection or inflammatory process.

2.7 Final Diagnosis and Outcome

After comprehensive evaluations and consultations with infectious disease and neuroimmunology specialists, the diagnosis of ongoing VZV meningoencephalitis was confirmed. The patient was started on valacyclovir, and after showing continued improvement, she was discharged on valacyclovir 1 g every 8 hours for 14 days. About six months after her VZV meningoencephalitis, she successfully underwent a lung transplantation without any complications.

3. Discussion

Varicella-zoster infections lead to serious complications such as postherpetic neuralgia, disseminated infections, and even death [7-10]. Disseminated VZV infections with central nervous system involvement after vaccine administration (live vaccines) are rare, with the vaccine strain found by PCR in less than 1% of VZV-positive CSF samples and less than 2% of VZV-positive non-CSF samples (e.g., skin biopsy, serum, respiratory swabs) [11]. In those who have previously received a live varicella vaccine, vaccine strain VZV can occasionally reactivate and cause HZ; however, literature is limited therefore it is difficult to determine whether the clinical presentation differs from that caused by the wild virus, making genotyping and strain surveillance essential [11, 12]. This patient is unlikely to have received live varicella vaccination as a child due to age, with routine childhood varicella vaccination being implemented in 1995, but it would be a consideration in those who may have received previous live vaccination. Recognizing the neurological complications of VZV is crucial in immunocompromised individuals, who may present differently, due to the associated morbidity and mortality and the potential benefit of antiviral treatment. This case demonstrates that severe central nervous system VZV reactivation can occur in immunocompromised hosts despite immunization with RZV, and vaccination does not confer complete protection from VZV reactivation. This patient's negative varicella IgG after RZV suggests that there was an inadequate immune response to the RZV series to provide adequate protection.

Individuals with immune-mediated diseases being treated with immunosuppressive drugs are the most rapidly expanding group of immunocompromised patients. The risks of HZ reactivation vary with the intensity of the immunosuppressive regimen, its duration, and, the particular agents mechanism of action [13]. Glucocorticoids are the most commonly prescribed class of drugs with immunosuppressive potential. Higher doses (>20 mg/day of prednisone or equivalent) increase the risk of HZ. Risk for HZ is elevated, but modestly, with many biologic agents, including tumor necrosis factor inhibitors, interleukin-6 inhibitors, B-cell-depleting agents, and T-cell co-stimulatory inhibitors. Janus kinase inhibitors pose the highest HZ risk among therapies, with risk varying by agent and increased with concomitant glucocorticoid use. The risk does not diminish over time, and a history of HZ increases the risk of recurrence. Patients on janus kinase inhibitors should be

prioritized for HZ prevention. The type 1 interferon inhibitor anifrolumab, used for systemic lupus, significantly increases HZ risk, especially in the first year, but the risk decreases with continued use, again these patients should be prioritized for HZ prevention. Awareness of the changing landscape of risks associated with immune-based therapy is critical to risk-mitigation strategies which remains the backbone of management [13].

It is recommended that all solid organ transplant (SOT) candidates have their varicella serologies assessed, and that all seronegative candidates be vaccinated prior to transplantation [4, 9]. Currently the IDSA and the Advisory Committee on Immunization Practice (ACIP), both recommend vaccinating those who are solid organ transplant candidates with VZV/HZ vaccination. The IDSA guidelines recommend use of the live-attenuated vaccine in patients ≥50 years of age who are not severely immunocompromised, at least 4 weeks prior to receiving immunosuppression; ACIP and the American Society of Transplantation recommendations indicate the use of the RZV over the live-attenuated vaccine due to superior efficacy for the general population >50 years of age and ability to be utilized in the immunocompromised populations [4]. Centers for Disease Control and Prevention guidelines recommend two doses of RZV in immunocompromised individuals ≥19 years old regardless of previous history of shingles or previous receipt of zoster vaccine live, with the second dose of RZV given 2-6 months after the first. However, the second dose can be administered 1-2 months after the first, with a shorter interval between doses to avoid vaccination during periods of more intense immunosuppression. Patients with autoimmune and inflammatory conditions should receive RZV prior to initiation of immunosuppressive medications when possible. If vaccination prior to initiation of immunosuppressive medications is not possible, RZV should be administered when immunosuppression is anticipated to be low. It is recommended that those who may be receiving anti-B cell therapies (such as rituximab) should receive RZV at least 4 weeks prior to the scheduled therapy initiation. Vaccination after transplant with live-attenuated vaccines is generally contraindicated due to the decline in cell-mediated immunity over time caused by prolonged immunosuppressive therapy in SOT recipients, which increases susceptibility to VZV reactivation and results in high morbidity and mortality.

During the early posttransplant period, prophylactic antivirals for cytomegalovirus and HSV, which are recommended by the American Society of Transplantation guidelines, also help prevent VZV reactivation. However, beyond this initial period and in those who do not receive cytomegalovirus prophylaxis, there have been no formal studies on the prevention of HZ or HZ encephalitis [4]. While there is routine HSV prophylaxis in all SOT, the duration and intensity varies depending on program, organ, and seropositivity. In immune-mediated diseases being treated with immunosuppressive drugs, treatment of HZ hinges on risk mitigation with vaccination and treatment of disease with antiviral drugs when it occurs. Currently, there are no consensus guidelines for prophylactic therapy in these populations [13].

Diagnosis of VZV infection is typically confirmed through lumbar puncture and CSF analysis, which often reveals lymphocytic pleocytosis along with positive viral culture, antibody tests, or PCR for VZV [9, 14-17]. CSF PCR assays facilitate earlier diagnosis, with VZV PCR demonstrating a sensitivity of 80%-95% and specificity exceeding 95% in immunocompromised patients [18]. In cases of VZV vasculopathy, CSF pleocytosis may be absent, and detecting anti-VZV antibodies in CSF can be more sensitive than VZV PCR. While prompt CSF sampling is ideal, quantitative serum VZV PCR can provide a presumptive diagnosis if CSF sampling is delayed or not possible. Additionally, VZV-

specific PCR analysis of saliva has proven to be more sensitive than plasma PCR in diagnosing HZ [18-21].

Treatment of infection involves reducing immunosuppression and administering intravenous acyclovir or valacyclovir [4]. Acyclovir-resistant strains have notably emerged in AIDS patients and bone marrow transplant recipients with prolonged acyclovir exposure. Alternative antivirals for acyclovir-resistant strains include foscarnet or cidofovir. While corticosteroids have been used in some cases to mitigate vasculitis effects, their use remains controversial [9].

In conclusion, VZV meningoencephalitis, though a rare complication of HZ, should be considered when neurological symptoms accompany CSF lymphocytic pleocytosis. This is particularly relevant in immunocompromised individuals, regardless of prior or recent vaccination status. It is important to recognize that VZV meningoencephalitis can manifest in atypical ways and may occur in the absence of a rash. Rapid progression of the disease is possible without timely intervention, making the prompt initiation of antiviral therapy essential to reduce the risk of severe complications and death. The intent of this case review is not to suggest that vaccination is the cause of the infection, nor to advocate against vaccination in immunocompromised individuals. Rather, it emphasizes the importance of maintaining a high index of suspicion for VZV meningoencephalitis in this population, even among those who have been vaccinated. It is important to recognize that immunocompromised hosts may not mount an adequate immune response to vaccines, potentially resulting in insufficient immunity to prevent infection. While the risk of encephalitis is generally lower in vaccinated individuals, it is crucial to keep this diagnosis higher on the differential list for immunocompromised patients.

Abbreviations

CSF	cerebral spinal fluid
HZ	herpes zoster
IDSA	Infectious Diseases Society of America
RZV	recombinant zoster vaccine
SOT	solid organ transplant
VZV	varicella-zoster virus

Author Contributions

Sara Evans PA-C was responsible for initial summary of case and primary draft, also responsible for revisions. Dr. Arjuna was project manager and was responsible for restructuring of case presentation. Dr. Moin was responsible for case formating and initial revisions.

Competing Interests

The authors have declared that no competing interests exist.

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