ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Disseminated Varicella-Zoster and Acute Liver Failure in a Patient With Crohn's Disease on Systemic Immunosuppression

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ABSTRACT

Approximately 4 million cases of varicella-zoster occur annually, most of which are self-limited and managed conservatively with supportive care with or without oral valacyclovir. However, varicella-zoster rarely disseminates leading to severe systemic illness affecting multiple organs. Disseminated varicella-zoster causes significant morbidity and mortality, particularly in immunocompromised individuals. In this study, we report a case of a 27-year-old immunosuppressed man who developed disseminated varicella-zoster infection culminating in multiorgan failure and death. We review the epidemiology, risk factors, diagnosis, prevention, and treatment of disseminated varicella-zoster.

KEYWORDS: Varicella zoster virus; acute liver failure; immunosuppression

INTRODUCTION

The varicella-zoster virus (VZV) is a human alpha herpes virus that historically has infected most children early in life causing the common, self-limited chickenpox. However, if contracted as an adult, primary VZV infection can cause serious and sometimes fatal complications. Following the primary infection, the virus remains latent in the dorsal root ganglion and can reactivate later as herpes zoster, commonly known as shingles.[1] Shingles typically manifests as a painful rash with fluid-filled blisters localized to one side of the body within a dermatome. It may also be present in noncontiguous dermatomes or bilaterally, termed herpes zoster duplex.[2] Risk factors of reactivation include older age, particularly in those aged older than 75 years; female sex; trauma to specific dermatomes; genetic predisposition; and immunocompromised states.[3]

Complications of localized shingles may include postherpetic neuralgia, facial nerve paralysis, and ocular shingles. In immunosuppressed patients, the reactivated virus may disseminate, spreading beyond the initial site of reactivation to include diffuse erythematous papules that subsequently evolve into clear, fluid-filled vesicles on an erythematous base. Dissemination can be associated with pneumonitis, hepatitis, disseminated intravascular coagulation, encephalitis, and death.[4]

Prevention of shingles and its complications is possible with the recombinant adjuvant zoster vaccine. The Centers for Disease Control and Prevention currently recommends this vaccine for all adults aged older than 50 years and immunocompromised adults aged 19 years and older.[5] Shingles is often treated with oral antivirals that are most effective when taken within 72 hours of symptom onset. In this study, we describe the case of a man with Crohn's disease taking immunosuppressive medications who developed disseminated VZV resulting in multiorgan failure and death. This case underscores the importance of vaccination against, and early recognition and treatment of, VZV in individuals with compromised immune systems.[5]

ACG Case Rep J 2025;12:e01611. doi:10.14309/crj.0000000000001611. Published online: February 10, 2025

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CASE REPORT

A 27-year-old man with a history of Crohn's disease on oral methotrexate 25 mg weekly and intravenous (IV) infliximab 10 mg/kg every 8 weeks for the past 3 years presented to the community emergency department with vomiting and right upper quadrant abdominal pain. On initial evaluation, a computed tomography (CT) scan of the abdomen and pelvis with IV contrast was normal. A complete blood count and comprehensive metabolic panel were significant for aspartate aminotransferase (AST) of 326 U/L, alanine aminotransferase (ALT) of 313 U/L, and total bilirubin of 1.2 mg/dL, which the treating providers initially attributed to steatotic liver disease or recent alcohol use. International normalized ratio (INR) was not checked during this emergency department visit. The patient was discharged home and encouraged to follow-up with his primary care physician to recheck his serum liver enzymes. Several hours after discharge, he noticed the onset of a vesicular rash starting on his face and spreading to his neck, arms, chest, and shoulders. On his way to an outpatient appointment the next day to have this evaluated, he experienced a new onset generalized tonic-clonic seizure, prompting his return to the emergency department.

On evaluation, his blood pressure was 147/84, heart rate was 56 beats per minute, and temperature was 36.5°C. He was found to be ill-appearing with a diffuse rash on the scalp, all extremities, and torso. Per the available medical records, the etiology of the rash was unknown and not discussed early within his hospitalization. A complete blood count and comprehensive metabolic panel revealed a platelet count of 105×10^9/L, AST of 2,115 U/L, ALT of 1,499 U/L, INR 3.3, total bilirubin 4.9 mg/dL, and alkaline phosphatase 761 U/L, and a urine drug screen was positive for cannabinoids and fentanyl. Further investigations including a head CT and spot electroencephalogram were unremarkable, but a brain magnetic resonance imaging suggested brainstem encephalitis, initially thought to represent some type of idiopathic encephalitis from his immunosuppressive agents. The patient was admitted to the neurosurgical intensive care unit and treated empirically with ceftriaxone and vancomycin. Serologic testing for other causes of acute liver failure including viral hepatitis and autoimmune hepatitis was negative. On hospital day 2, the diagnosis of acute liver failure was made based on profoundly elevated liver enzymes, elevated INR to 3.3, and hepatic encephalopathy. He also developed hemodynamic shock requiring vasopressors on hospital day 2 that progressed over the next 2 days and the eventual need for mechanical ventilation. At this point, the medical team believed that the patient was suffering from indeterminate acute liver failure with superimposed bacterial infection. Therefore, transfer to our tertiary care medical center with liver transplant capability was pursued; however, no beds were available at the requested time. Our transplant hepatologist consulted with the referring medical team by phone and recommended starting N-acetylcysteine, monitoring for signs of increased intracranial pressure, and continuing broad spectrum antibiotics and antiviral agents. Detailed discussions of liver transplantation were deferred due to high concern that the patient had an active infection.

On hospital day 3, he remained acutely ill and encephalopathic and underwent a lumbar puncture, which revealed a positive polymerase chain reaction (PCR) test for VZV in the cerebrospinal fluid, confirming a diagnosis of disseminated VZV. On hospital day 3, IV acyclovir was started. On hospital days 4 and 5, he experienced acute renal failure, disseminated intravascular coagulation, bacteremia (methicillin-sensitive Staphylococcus aureus and Actinomyces), and tachyarrhythmia that contributed to the delay in transfer to our tertiary medical center.

When he was transferred to our quaternary medical center on hospital day 7, his laboratory results showed white blood cell count of 30×10^9/L, hemoglobin of 8.6 g/dL, and platelet count of 102×10^9/L, and severe liver dysfunction was indicated by elevated total bilirubin of 8.8 mg/dL, AST of 9,627 U/L, ALT of 3,155 U/L, and alkaline phosphatase of 950 U/L, along with an INR of 3.79 and lactate 14 mmol/L. Chest/abdominal/pelvic CT imaging revealed multilobular peribronchovascular patchy ground glass opacities and nodular centrilobular consolidation in the lungs, consistent with a diffuse viral pneumonitis, along with proctitis, and complete thrombosis of the portal venous system with minor ascites. At this time, due to systemic viral and bacterial infections, he remained in multiorgan failure including encephalitis, pneumonitis, liver failure, and renal failure. He was not a candidate for liver transplantation because of active, uncontrolled infection and hemodynamic instability. Despite intensive supportive care by a multidisciplinary team of specialists in infectious diseases, hepatology, hematology, and pulmonary critical care, the patient's condition deteriorated, and he died on hospital day 8.

DISCUSSION

This patient presented with disseminated VZV, which rapidly progressed from a diffuse rash to multiorgan failure within 24 hours. The death of this patient was presumed to be caused by disseminated VZV infection with secondary bacteremia, leading to multisystem organ failure. However, the lack of information about his prior exposure to VZV or the varicella vaccine as a child makes it difficult to know whether his illness was due to a disseminated primary VZV infection or a disseminated reactivation of VZV. Either way, this case emphasizes the need to educate immunosuppressed patients on warning signs of disseminated VZV, such as a new erythematous, pruritic, or painful rash. Although it is unknown whether earlier recognition and treatment of his VZV disease could have altered the outcome of his illness, this case highlights the need for clinicians to have a high index of suspicion for disseminated VZV infection, particularly in immunocompromised patients, to optimize the chances of survival.

Disseminated VZV disease can occur during primary infection or reactivation. Disseminated shingles is defined by at least 20 skin lesions in over 2 contiguous dermatomes.[6] Disseminated VZV often involves visceral organs and can lead to complications such as encephalitis, hepatitis, and pneumonitis.[7] In this case, the patient developed encephalitis, pneumonitis, acute renal failure, acute liver failure, and a secondary bacterial infection. In immunocompromised individuals, the incidence of VZV reactivation is 10 times higher than that in the general population. A study reported 56 cases of disseminated VZV among renal transplant recipients on systemic immunosuppression between 1985 and 2011. Of these cases, 17 resulted in death, while 39 patients survived.[8] Most cases (70%) occurred within 5 years of transplantation, and risk factors of mortality included the development of visceral involvement and the use of azathioprine.[8]

Although herpes zoster typically resolves on its own in immunocompetent individuals, it can occasionally lead to complications necessitating systemic steroids, opioids, and hospitalization. Thus, early identification may be of benefit. In cases where the diagnosis is uncertain based on clinical presentation, PCR testing from a vesicular fluid swab or scraping of lesion cells is recommended.[9] Culture and serologic testing are slower and less sensitive methods than PCR and, therefore, are not routinely used to diagnose herpes zoster.[9]

Early diagnosis is known to be important when herpes zoster ophthalmicus, oticus, or other neurologic complications are present, as promptly starting treatment in these conditions may prevent more serious complications.[10] Given the high morbidity and mortality of visceral varicella zoster (VZV), hospitalization should be pursued early in these cases.[11] Though not life threatening, postherpetic neuralgia is another complication of herpes zoster.[12] In one study, starting valacyclovir within 48 hours of the onset of the herpes zoster rash reduced the duration of postherpetic neuralgia.[13] However, another study showed that early antiviral therapy did not reduce the incidence of postherpetic neuralgia.[12] In general, treatment of herpes zoster is recommended to facilitate healing of cutaneous lesions, provide analgesia, prevent progression to complicated disease, and decrease risk of transmission.[14] The literature supports early initiation of antiviral medications to prevent complications of herpes zoster in all patients who have uncrusted lesions when presenting within 72 hours of symptom onset and at any time if immunocompromised.[15]

Hepatitis and acute liver failure, as was the case in this patient, represent rare but serious complications of disseminated VZV. This is documented in several case reports. In the first case, a 66-year-old woman with dermatomyositis receiving mycophenolate mofetil and prednisone developed a rapidly progressing rash accompanied by significantly elevated liver enzymes. She was diagnosed with acute liver failure from disseminated VZV, and despite receiving acyclovir and intensive supportive care, her condition deteriorated rapidly, resulting in death.[16] This case report also summarized the literature, including 8 other case reports of patients with acute liver failure from disseminated VZV, ranging from 15 to 64 years old and including those with and without underlying immunosuppression.[16]

Similarly, a retrospective study revealed an increased incidence of visceral VZV infection among recipients of allogenic hematopoietic stem cell transplants. Among 2,411 transplanted patients, 20 developed visceral VZV infection, characterized by cutaneous eruptions accompanied by severe abdominal pain but with normal CT findings. Seventeen of these patients were undergoing immunosuppressive therapy, and 4 of these 20 patients died. All 4 patients who died had fulminant hepatitis and multiorgan failure. This study emphasizes the importance of early identification of visceral VZV infection and the prompt treatment with acyclovir, which correlated with a reduction in mortality rates.[17]

Acute liver failure, characterized by acute loss of hepatic function associated with coagulopathy and altered mental status, is a life-threatening condition that is associated with poor outcomes when caused by disseminated VZV.[17] Most patients described in the aforementioned case reports were immunocompromised, highlighting the heightened risk of morbidity and mortality associated with visceral involvement and acute liver failure from VZV infection.

Vaccination against VZV has been available in the United States since 2006. The single-dose live-attenuated vaccine is no longer available in the United States and has been replaced by the more effective two-dose, recombinant subunit vaccine. Studies indicate that the recombinant vaccine is 97% effective in immunocompetent adults aged 50–69 years and 91% effective in individuals older than 70 years.[18] In immunocompromised adults, efficacy of the recombinant vaccine ranges from 68 to 91%. Regardless of whether one has previously received the older live zoster vaccine, the Centers for Disease Control and Prevention recommends that 2 doses of the recombinant vaccine be administered 2–6 months apart for adults aged 50 years and older and for immunocompromised individuals aged 19 years and older.[18] Contraindications to receiving the recombinant zoster vaccine include active shingles infection and pregnancy.

A significant hurdle in implementing a vaccination program is the challenge of determining immunization status and accessing historical vaccination records. There is currently no systematic way to track individual vaccination status throughout the entire United States. Unfortunately, information about this patient's VZV vaccination status is unknown, so we are unable to assess the effectiveness of the vaccine in this case or fully understand whether this represented primary or secondary VZV.[19]

Despite presenting to the emergency department within 5 hours of the onset of his rash and receiving acyclovir within 72 hours,

the patient's condition rapidly deteriorated and he died of multisystem organ failure including acute liver failure after 8 hospital days. This case report highlights the morbidity and mortality linked to disseminated VZV among individuals with compromised immune systems. Given the high efficacy of the recombinant zoster vaccine, vaccination could have potentially prevented this patient's death.

DISCLOSURES

Author contributions: B. Shore: chart review, literature review and creation of initial draft of case report; JJ Hansen: Literature review, revision of manuscript; OK Fix: Literature review, revision of manuscript. JJ Hansen is the article guarantor.

Financial disclosure: None to report.

All attempts have been exhausted in trying to contact the patient's health care decision maker (mother) for informed consent to publish their information, but consent could not be obtained.

Received September 27, 2024; Accepted January 9, 2025

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