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Case report

A rare case of acute liver failure due to disseminated Varicella-Zoster Virus (VZV) infection

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ABSTRACT

Varicella zoster virus (VZV) is a human alpha herpes virus that typically manifests in humans with two distinct cutaneous phenotypes: primary varicella, or chickenpox, and secondary reactivation, or Shingles, after establishing latency in the cranial and dorsal root ganglia. VZV infection can present with rarer manifestations including encephalitis, pneumonia, hepatitis, myocarditis, and nephritis. Immunocompromised populations are at the greatest risk for cutaneous and visceral dissemination. The progression of VZV hepatitis to acute liver failure is exceedingly rare, with very few published cases in the literature. In the following case, we report the initial presentation and clinical manifestations of an immunocompromised patient who presented with vesicular skin findings and elevated transaminases, who quickly progressed to acute liver failure, and had postmortem findings of disseminated VZV infection.

Introduction

Varicella zoster virus (VZV) is one of eight herpes viruses known to infect humans [1]. After initial infection, the virus establishes latency in the cranial and/or dorsal root ganglia [2]. VZV reactivation (Zoster) classically manifests as a painful vesicular rash spread over a specific dermatome [3], with the most common complication being long-standing neuralgia. Less often, disseminated disease can occur, characterized by the involvement of 3 or more dermatomes, or the presence of more than 20 vesicles outside of the primary and adjacent dermatomes [4]. Neurologic and extraneural sequelae can also develop, including ocular involvement, cranial nerve palsies, meningoencephalitis, and vasculopathy [2]. Immunocompromised populations, in particular hematopoietic stem-cell and solid organ transplant recipients, appear to be most at risk for cutaneous and visceral dissemination [5–7]'. These complications confer a high mortality [8]. VZV hepatitis is among the most feared complications in this population, and numerous deaths have been reported [9–11]. Here we report a fatal VZV hepatitis case in a patient with plasma cell dyscrasia and autoimmune hemolytic anemia on many immunomodulatory therapies.

Case presentation

The patient is a 58-year-old male with a medical history of mixed warm and cold autoantibody subtype autoimmune hemolytic anemia, Waldenström's macroglobulinemia versus IgM myeloma, and hypogammaglobulinemia who presented with complaints of acute on chronic fatigue and development of lesions on his skin. To treat his autoimmune hemolytic anemia and suspected IgM myeloma, our patient was immunosuppressed with multiple agents including corticosteroids (prednisone 10 mg daily, dexamethasone 40 mg given 3 days monthly in 28-day cycles), sutimlimab-jome every 2 weeks, and carfilzomib given 3 days monthly in 28-day cycles. Prior treatment regimens for his Waldenström's macroglobulinemia in the years preceding his presentation included lenalidomide/bortezomib, daratumumab/pomalidomide, bendamustine/rituximab, cyclophosphamide/vincristine/prednisone (CHOP), and rituximab/cyclophosphamide/vincristine/prednisone (R-CHOP), all of which failed to produce monoclonal plasma cell remission. On initial examination, patient was afebrile, nontoxic appearing, and oriented to place and time. Physical exam findings revealed jaundice, scleral icterus, and multiple vesicular lesions scattered on the scalp and torso. Initial liver tests revealed aspartate

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aminotransferase (AST) 466 U/L, alanine aminotransferase (ALT) 657 U/L, alkaline phosphatase 163 U/L, total bilirubin 3.7 mg/dL, and direct bilirubin 1.8 mg/dL. Computed tomography (CT) scan of the abdomen showed splenomegaly, gallbladder stones and sludge, but no reported liver architectural abnormalities. Magnetic resonance cholangiopancreatography (MRCP) showed no hepatobiliary abnormalities, and a liver biopsy was performed for evaluation of hepatocellular disease. Concern for herpes simplex virus or VZV hepatitis prompted initiation of acyclovir 10 mg/kg every 8 hours. On hospital day 2, transaminases increased to AST 1209 U/L, ALT 1463 U/L, alkaline phosphatase 160 U/L, total bilirubin of 7.1 mg/dL, and direct bilirubin 5.0 mg/dL. The patient became acutely encephalopathic and his international normalized ratio (INR) increased from 1.2 to 1.4. At family and patient request of palliative care evaluation, shared decision was made to pursue comfort measures only rather than undergo further invasive medical management. Acyclovir was discontinued after approximately 24 hours of therapy. The patient passed away surrounded by his family on hospital day 3. PCR for VZV from skin and blood both resulted positive. In addition, results from the liver biopsy specimen showed intracellular inclusions and geographic hepatocyte necrosis consistent with viral hepatitis (Fig. 1A, 1B), and the specimen was in situ hybridization positive for VZV (Fig. 2). Ultimately, it was determined that the patient passed away from acute liver failure due to disseminated VZV hepatitis.

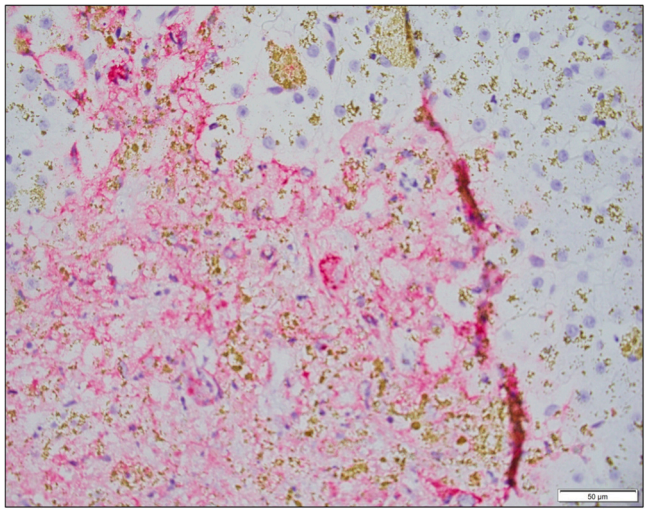

Fig. 2. High power view showing hepatocellular necrosis, VZV (represented by the pink-red intracellular signal), and brown gold iron pigment (original magnification 40X; in situ hybridization for VZV).

Discussion

The case above demonstrates the rapidly progressive and potentially fatal course of disseminated VZV hepatitis leading to acute liver failure. The etiology of this case is likely due to reactivation rather than primary infection, as the patient's family confirmed varicella infection during childhood. VZV reactivation is thought to occur as a result of cell-mediated immunity being diminished beyond a certain threshold [3]. The reported incidence of disseminated varicella is quite variable, ranging from 0–0.5 % in immunocompetent populations to as high as 20.6 % in select immunocompromised populations, according to one study [12].

Multiple risk factors have been identified with zoster reactivation. Age is an important risk factor [5], and may be attributable to declines in cell-mediated immunity with age [13]. Immunocompromised populations are known to be at risk for reactivation, and transplant recipients are at particular risk for disseminated Zoster [5–7]. Numerous medical therapies have a documented association with VZV, namely corticosteroids, biologics (specifically non-TNF-α inhibitors) and nonbiological disease-modifying antirheumatic drugs [14]. Certain chemotherapeutic agents such as carfilzomib also have a documented association as discussed below. Our patient was unfortunately burdened by multiple risk factors, namely lymphoproliferative disorder, chemotherapy, and corticosteroid use. While our patient was also on a non-TNF biologic agent, further investigation needs to be done specifically regarding complement inhibitors (eg sutimlimab) and their relationship with VZV activation.

The diagnosis of VZV is typically made clinically based on the presence of characteristic skin lesions, although adjunctive testing can be utilized when clinical uncertainty is present. Polymerase Chain Reaction (PCR) of clinical specimens is the gold standard for laboratory diagnosis, and is well recognized for its high sensitivity and specificity [15,16]. Serologic testing is typically of limited value; although IgG antibodies can help ascertain whether an individual has had previous exposure to VZV and/or response to vaccination [16,17]. Viral culture is also limited in its use due to extended turnaround time [16]. In our case, the diagnosis of disseminated VZV was made posthumously with the return of VZV from skin, blood, and liver biopsy specimen. Liver biopsy was pursued given the patients rapid development of acute liver failure without a known cause at the time.

VZV hepatitis is a particularly rare complication of varicella infection. To date, few cases of acute liver failure due to VZV hepatitis have been published, with most patients undergoing immunosuppressive therapy at the time of VZV diagnosis. An early case documented a 40-year-old male with acute myeloblastic leukemia who underwent chemotherapy and a bone marrow transplant who received IV acyclovir and VZV immunoglobulin but expired on hospital day 16 [9]. Maggie et al. reported a 49-year-old male who was taking a short course of prednisone presenting with signs of hepatitis and found to be VZV serology positive and given IV acyclovir and VZV immunoglobulin [10]. He quickly developed signs of acute liver failure and liver transplant was

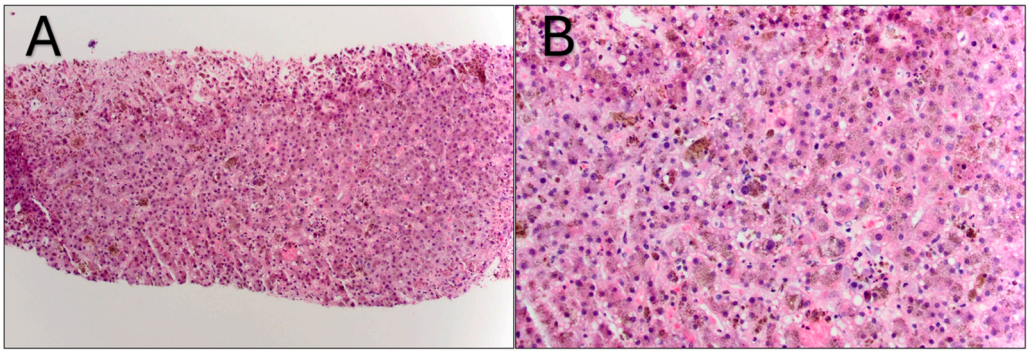

Fig. 1. (A) Low power view (original magnification 10X) and (B) medium power view (original magnification 20X) of H&E stained liver biopsy showing focal hepatocellular necrosis, intact liver sinuses and cords, abundant sinusoidal and hepatocellular iron, mild periportal chronic and rare neutrophils.

considered; unfortunately, the patient expired on day 7 of hospitalization [10]. Our case most resembles that of Saitoh et al., who reported a 47-year-old male with IgD multiple myeloma who underwent reduced-intensity stem cell transplantation and was undergoing salvage chemotherapy with doxorubicin and dexamethasone due to increased IgD levels and new bone lesions [11]. After presenting with fatigue, that patient was found to have developed fulminant hepatitis and passed away 4 days after presentation, with liver autopsy showing extensive foci of necrosis throughout the parenchyma, and an immunohistopathological evaluation showing VZV positive hepatic cells [11].

Intravenous acyclovir is the mainstay of treatment for disseminated zoster, given its evidence in reducing disease progression and increasing the rate of clearance [18,19]. While some case reports have documented positive outcomes with the addition of intravenous immunoglobulin (IVIG) [20,21], to our knowledge there are no consensus guidelines advocating for the routine use of IVIG for the treatment of complicated zoster infections.

The high degree of morbidity and mortality in patients with disseminated zoster highlight the need for further efforts targeted at disease prevention. The recombinant glycoprotein E vaccine (ie, recombinant zoster vaccine [RZV]) is approved for immunocompetent individuals greater than 50 years of age in addition to individuals $\geq$ 18 years who are or will be at increased risk of zoster infection due to immunosuppression. Unfortunately, our patient's multiple comorbidities, including uncontrolled autoimmune disease, active lymphoproliferative disorder, and ongoing glucocorticoid use, likely precluded him from receiving the zoster vaccine.

Antiviral prophylaxis for prevention of zoster reactivation in select immunocompromised populations is a well-known practice. Hematopoietic stem cell transplant recipients at risk for Varicella routinely undergo prophylaxis with agents such as acyclovir or valacyclovir [22]. Solid organ transplant recipients not already receiving prophylaxis against cytomegalovirus are recommended to receive short-term prophylaxis against VZV [4]. Carfilzomib-based therapies have been associated with an increased risk in herpes zoster [23]. The National Comprehensive Cancer Network calls for consideration of prophylaxis in this patient population, but does not go so far as making a formal recommendation [23]. Our patient did not receive antiviral prophylaxis; empiric therapy with IV acyclovir started on day 1 but was unfortunately ineffective. Given his significant comorbidities and medical wishes for comfort measures, the decision to pursue VZV immunoglobulin and liver transplant were deferred.

The case describes fulminant hepatic failure as a rare but devastating complication of zoster reactivation. The high morbidity and mortality of this complication reinforces the need for constant vigilance for this condition when thinking about treatment and prevention of infectious comorbidities, particularly in the immunocompromised host.

CRediT authorship contribution statement

Feldman Harris: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Newstein Michael C.:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Mangano Mark:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Neale Matthew:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Batra Ajay:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Author contributions

HTF, MCN, and AB conceived the study design. Literature review was conducted by HTF and MN. HTF and MN drafted the initial manuscript. MM interpreted the pathology slides. All authors contributed intellectually to the final manuscript.

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Consent

The patient's healthcare proxy and family members gave consent for all or any part of the manuscript to appear in print and online versions. They have reviewed all materials or been offered the opportunity to review all materials, but waived their rights to review.

Ethical approval

Written informed consent for publication of the case report (including images) was obtained by the patient's healthcare proxy. A copy of this written consent can be made available to the journal upon request.

Co-Authorship

HTF and MNN will serve as co-first authors for the manuscript. A "*" is designated at the end of each name with "*" to signify this co-authorship.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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