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Case report

Varicella Zoster aseptic meningitis: Report of an atypical case in an immunocompetent patient treated with oral valacyclovir

Martin Gnoni[a,1], Kamran Zaheer[a,2], Melinda M. Vasser[a], Monider Singh[b,*], Aman Ajmeri[b], Stephanie R. Harter[b], Abdul Mughees Rana[b], Rodrigo Aguilar[b]

[a] Our Lady of Bellefonte Hospital, 1000 St Christopher Dr, Ashland, KY 41101, United States
[b] Marshall University, MU Internal Medicine Residency Program, 1249 15th Street, Huntington, WV 25701, United States

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ABSTRACT

Varicella Zoster when described has the typical presentation of a dermatomal distribution of a rash and can further lead to CNS complications. This can be treated accordingly with the proper protocol, but if the presentation is atypical and the protocol is challenged or changed per specific patient outcomes, new developments can occur. Here we present a case of a 29-year-old Caucasian female that presented to the emergency department with headache, photophobia, and chills for 5 days. She was previously healthy and immunocompetent; CSF PCR analysis revealed a VZV infection causing acute aseptic meningitis with no shingles rash eruption on physical examination. The patient was not willing to stay hospitalized for the duration of the treatment. This gave us an opportunity to treat her with an oral, rather than IV, antiviral. The patient was successfully treated with oral valacyclovir 2 g Q6H after only receiving two days of IV acyclovir. To the best of our knowledge, this is the first reported case of a patient with VZV-associated meningitis successfully treated with oral valacyclovir.

Introduction

Viral meningitis accounts for approximately 26,000 to 42,000 hospitalizations each year in the United States [1], affecting mainly infants younger than one year, children 5–10 years of age, and the immunocompromised [2]. Varicella Zoster virus is responsible for about 11% of those cases [3]. Varicella can infrequently lead to Encephalitis resulting in seizures and coma (estimated 1.8 per 10,000) [2]. Other rare but serious complications of VZV include transverse myelitis, guillain-barré syndrome, thrombocytopenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, and hepatitis [2,4].

VZV, a member of the Herpesviridae family, is an enveloped, double stranded, linear DNA virus with a capsid arranged in an icosahedral form. VZV is a neurotropic virus that infects nearly all humans. When a person contracts VZV they initially develop varicella. After the episode, the virus will remain latent in the cranial nerve, dorsal root and autonomic ganglions [4]. In most cases the virus stays dormant for decades until the host's VZV-specific immunity declines, allowing the virus to reactivate spontaneously. This results in shingles {herpes zoster} and is typically characterized by pain and a rash in a dermatomal distribution. Some cases have been reported in the literature of reactivation of VZV with direct invasion of cranial nerves [5] in otherwise immunocompetent patients. In particular, one case exhibited involvement of CN VI with increased intracranial pressure and bilateral papillary edema [6]. This shows the high variability in presentation in particular atypical types.

Traditionally VZV meningitis has been treated with IV acyclovir in accordance with the Infectious Disease Society of America (IDSA) treatment guidelines [7]. Currently there are no published studies about treatment of complicated infection of VZV with oral valacyclovir. However, there are several papers presenting the argument that 1 g valacyclovir Q6H can achieve the same or better CNS concentration as 500 mg acyclovir given IV TID [7–11].

We report a case of a previously healthy immunocompetent 29-year-old female with a reactivated VZV infection causing acute aseptic meningitis with no rash present. In addition, she also demonstrated late involvement of CN VIII. To the best of our knowledge, this is the first case of a patient with VZV aseptic meningitis, which was successfully treated with oral valacyclovir.

* Corresponding author.
E-mail addresses: tinchoinfectologo@gmail.com (M. Gnoni), zaheer@marshall.edu (K. Zaheer), DOmvasser@osteo.wvsom.edu (M.M. Vasser), singhm@marshall.edu (M. Singh), ajmeri@marshall.edu (A. Ajmeri), sharter@osteo.wvsom.edu (S.R. Harter), mugheesrana90@hotmail.com (A. Mughees Rana), aguilarcampo@marshall.edu (R. Aguilar).
[1] Permanent Address: Bellefonte Infectious Disease Associates, 400 St. Christopher Dr. Ashland, KY 41101, United States.
[2] Permanent Address: Marshall University, MU Internal Medicine Residency Program, 1249 15th Street, Huntington, WV 25701, United States.

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Case report

A 29-year-old Caucasian female presented to the emergency department with headache, photophobia, and chills for 5 days. She described the headache as a sharp, throbbing, constant pain that radiates to her occipital area, reporting some relief with NSAID use. She had mild diarrhea for 2 days prior to the onset of her headache. She also complained of mild stiffness of her neck with neck flexion causing pain to radiate down her spine with no prior history of migraines. On further questioning, she mentioned a possible insect bite of unknown origin on her right gluteal area about three days prior to the onset of her symptoms. She denied recent hiking or tick bites. The patient did not report having fever, abdominal pain, paresthesia, or hearing loss and said her three children were ill with diarrhea and mild fever before the onset of her own symptoms. The patient was not taking any daily home medications, including herbal supplements, OTC medications, or birth control. Her past medical and surgical history was unremarkable. She did not have any pertinent family history.

On examination, the patient was alert and oriented with signs of discomfort. Her vital signs were within normal limits. She had no fever and her BMI was 31.32 kg/m^2. There was a 0.5×0.5 cm rash with an erythematous base and grouped vesicles in the right gluteal area. Although it had features similar to a varicella eruption, suspicion was low due to the small size, lack of dermatomal distribution and presentation at a young age. It was ultimately diagnosed as a rash due to an insect bite. She had mild neck stiffness but normal range of motion. No signs of meningeal irritation were found. CN II through XII were grossly intact, and the rest of the neurologic examination was normal.

Her CBC showed a WBC count of 7.8 K/uL (67% neutrophils, 24% lymphocytes, 8% monocytes, 1% eosinophil, and 0% basophils), and the inflammatory markers (CRP and sedimentation rate) were normal. CSF analysis showed elevated protein levels of 157 mg/dL and a WBC count of 454/cu mm. Varicella Zoster was detected by PCR in the CSF viral panel. The respiratory viral panel was negative, and no bacterial antigen was detected in the CSF. Two peripheral sets of blood cultures had no growth after two days. Tests were negative for West Nile Virus, HIV, HCV, and HBV. The urine drug screen for commonly abused drugs was negative. After careful consideration of the patient's history and laboratory studies, we diagnosed her with aseptic meningitis due to VZV infection.

The patient was informed of her diagnosis and started on IV acyclovir 500 mg Q8H. The treatment plan according to IDSA guidelines required her to receive IV acyclovir as an inpatient for 10–14 days. However, she refused to stay in the hospital for that duration, so after careful review of the literature she was given the option to take valacyclovir 2 g Q6H for 14 days. She agreed and was discharged home, with a plan for close follow up in the clinic. She was seen in the clinic 3 days after discharge. She was asymptomatic and was told to continue her treatment. On day 10 after discharge the patient was seen in the office with a new symptom of decreased hearing in her right ear and reoccurrence of her headache. HEENT exam was normal. She was sent to the emergency department for a repeat lumbar puncture. The analysis of the CSF was normal, and the PCR was negative for VZV. The patient was advised to finish the last 4 days of her valacyclovir, and report to the office or emergency department if she had new symptoms or worsening hearing. She was seen in the office one week after she finished her treatment, at which time she reported no new symptoms and partial recovery of her hearing.

Discussion

Reactivated VZV can cause wide varieties of neurologic diseases [4,12], including aseptic meningitis even in otherwise healthy and immunocompetent patients. There are reports of several cases where patients with no rash were diagnosed with VZV meningitis. With the advent of CSF PCR, these atypical presentations are being more frequently encountered by clinicians. A systematic study on this topic may direct a need for reclassifying it as no longer atypical. It is important to suspect and test for VZV if a patient presents with aseptic meningitis, because with the development and availability of new technologies, such as antibody and PCR testing [5,13], it is often relativity easy to confirm the diagnosis and give patients the appropriate treatment. Currently, the IDSA recommendation for VZV-associated meningitis is to give the patient IV acyclovir 10–15 mg/kg Q8H for 10–14 days [14]. However, this usually requires hospitalization, exposing the patient to increased treatment costs and risks such as hospital-acquired illnesses.

Here we are reporting a case of a patient successfully treated with oral valacyclovir 2 g Q6H after only receiving two days of IV acyclovir. The patient in this case was a previously healthy, immunocompetent adult who was not willing to stay hospitalized for the duration of the treatment. This gave us an opportunity to treat her with an oral, rather than IV, antiviral. To the best of our knowledge, we believe that this is the first reported case of a patient with VZV-associated meningitis successfully treated with oral valacyclovir. However, more research needs to be done on this topic as the reported number of patients successfully treated orally is unclear.

Valacyclovir in its oral form has the same antiviral activity as Acyclovir because it is a prodrug that is metabolized into Acyclovir in the intestine and liver [15]. When treating a patient with extensive VZV infection that involves the CNS, one has to take into account different pharmacokinetic parameters of the specific drug chosen which includes the 50% inhibitory concentration [IC50], possible drug concentration in the CSF and their potential adverse effects [7]. When considering antivirals, the concentration should ideally exceed the IC50 of the target pathogen in CSF/CNS [15]. Oral acyclovir has a poor bioavailability of 26% and a CNS penetration of only 20% [7]. These two factors combined make oral acyclovir a poor choice, and it should not be used for the treatment of CNS VZV infections [7,8]. The IC50 for most VZV isolates is 0.12–0.18 ug/mL [15]. The bioavailability of Valacyclovir is 50%, and when it is given at a dose of 1 g(PO) Q8H, it reaches a concentration of 0.79 ug/mL in the CSF [7]. To diminish VZV strain growth, a dose of 2 g Q6H is required [7,10].

Treatment with IV acyclovir is associated with an increased cost of health care, but it also has significantly more side effects compared to oral valacyclovir, including CNS toxicity and, rarely, permanent CNS and renal damage [16]. That being said, IV acyclovir, tends to continually be used even though it has been shown that valacyclovir is tolerated better by patients and has substantially less side effects [10]. Since patients do not need to be hospitalized for the duration of the entire treatment, it could result in significantly less costs compared to IV acyclovir.

Conclusion

VZV meningitis was previously considered to be a rare cause of aseptic meningitis due to the lack of appropriate detection tests; however, VZV is now well known to be a cause of aseptic meningitis in adults as a result of new developments in diagnostic techniques such as antibody and PCR testing [5]. In addition, VZV associated meningitis can present with or without the typical vesicular dermatomal rash. Clinicians have to keep many variable presentations in mind and in doing so choose the appropriate treatment for that specific patient. Currently IV acyclovir is the recommended treatment, but oral valacyclovir should be considered in patients with no other risk factors. For the treatment of VZV

associated meningitis, oral valacyclovir should be dosed at 2 g Q6H for at least 10–14 days, but some patients may require up to 21 days of therapy [7].

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