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RENAL DOSE ADJUSTMENT MANAGEMENT FOR HERPES ZOSTER IN IMMUNOCOMPROMISED PATIENT WITH RENAL IMPAIRMENT: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Background: Herpes zoster is a reactivation of varicella-zoster virus that is characterized by a painful dermatomal vesicle eruption. Herpes zoster can bring several burdens including a painful rash and complications such as herpetic neuralgia and other neurological disorder. Herpes zoster commonly affects persons with decreased immunity levels which can caused by several conditions including malignancy. Multiple myeloma is one of the haematological malignancies commonly associated with renal impairments. Acyclovir is excreted in an unchanged form through renal, thus in patients with renal impairment could decrease the excretion level and can increase the possibility of renal toxicity. **Case Presentation:** We present a case report of a 46-year-old herpes zoster patient with multiple myeloma and renal impairment. The renal dose adjustment for acyclovir was done in this patient becomes 800mg three times daily. One week after the administration of acyclovir this patient showed remarkable results, there was no new lesion was found. This patient resolved after 10 days of renal dose adjustment of oral acyclovir and continued the multiple myeloma treatment on day fourteen. **Conclusion**: The management of herpes zoster infection in a patient with multiple myeloma commonly accompanies with renal impairment thus the consideration of adjusting the dose for renal impaired condition is important to reduce the possibility of renal toxicity in concordance with maintaining its adequate dose to prevent the possibility of complication

INTRODUCTION

Herpes zoster is a viral infection characterized by a painful dermatomal rash cause by the reactivation of varicella zoster virus (VZV) that is dormant in the dorsal root of the ganglion. The global prevalence of herpes zoster nowadays increasing, and it was found to be more common in elderly and immunocompromised persons (due to disease or therapy).(San Martin et al., 2023)

Herpes zoster could bring several burdens towards its possessors, it can cause several complications with the most common accompanying complication being post-herpetic neuralgia which could affect the quality of life.(Chen et al., 2024) Herpes zoster can also cause economic burdens due to the high health utilization and medical cost and it can indirectly affect the productivity of the possessors.(San Martin et al., 2023)

The mainstay treatment for herpes zoster is early intervention with antiviral, such as acyclovir.(San Martin et al., 2023) Acyclovir has long been known to be one of the safest and most effective antivirals for varicella infection including herpes zoster. Regardless of its safety and efficacy, it can cause crystallization nephropathy, thus causing renal failure.(Perazella, 2003; Sawyer et al., 1988) Dose

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regulation in patients with kidney disease is crucial, considering the limited kidney excretion of acyclovir, which increases the risk of neurotoxicity. However, inadequate acyclovir dosing can also increase the risk of encephalitis.(Wibisono, 2020) Hereby we reported a case report of a herpes zoster infection in immunocompromised patients with renal impairment, the importance, and the literature review of renal dose adjustment.

CASE REPORT

A 46-year-old woman came to the outpatient clinic of dermatology and venereology with a chief complaint of multiple painful blisters on her right chest. The blister emerged on her right trunk in the last two days prior to the visit. Initially, there was only a small number of red papules but between two days the red papules evolved to blister started to multiply progressively and spread to her right back torso. The blister was accompanied by fever, malaise, and a burning-like sensation and stabbing sensation on the skin lesion. The patient was diagnosed with multiple myeloma stage III in 2023 and is currently under the first cycle of bortezomib. There was no history of diabetes mellitus and hypertension. The patient has a history of varicella during childhood.

The vital signs in this patient were stable but there was an increasing heart rate of 120 beat per minute with a VAS score found to be 5-6. On the dermatological status, there were multiple clustered vesicles on an erythematous-based macule with normal skin between clusters that were distributed within dermatomal T5-T7. Multiple giant cells were found in the Tzank smear examination result. Her laboratory results there was decreasing hemoglobin level of 8.6 g/dl, a low platelet level of 126.000/mm^3, and increasing renal function test bool urea/ serum creatinine were 40/3.1 mg/dl. We calculated the patient's estimated glomerular filtration rate (e-GFR) and the result was 17 ml/min. This patient was then assessed with Herpes Zoster Thoracalis T5-T7 Dextra, Multiple Myeloma stage III on Bortezomib cycle 1, acute kidney injury on chronic kidney disease.

This patient has treated with acyclovir 800 mg three times daily for ten days, paracetamol 500 mg three times daily for fever and pain, wound care compress with normal saline, and fusidic acid 2% cream twice daily on skin erosions, the chemotherapy was postponed until the infection resolved. One week after the treatment there was no new blister leaving multiple ulcers on her skin, and the VAS score was reduced to 2-3. We educate the patient on the possibility of recurrence and the importance of vaccination to prevent recurrent episodes.

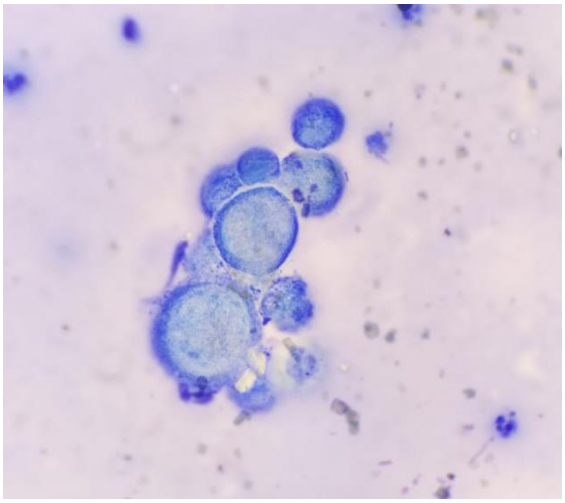
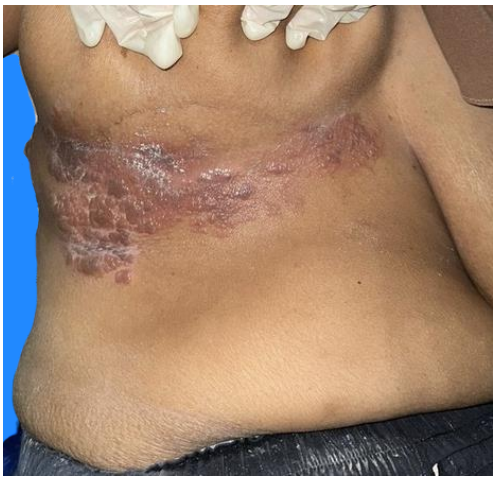


Figure 1. Multiple giant cells on Tzank smear examination.



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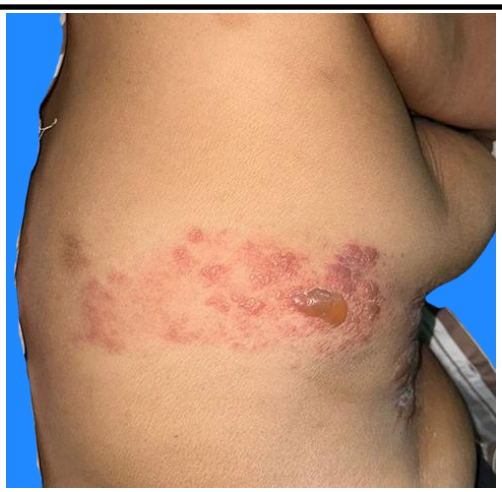
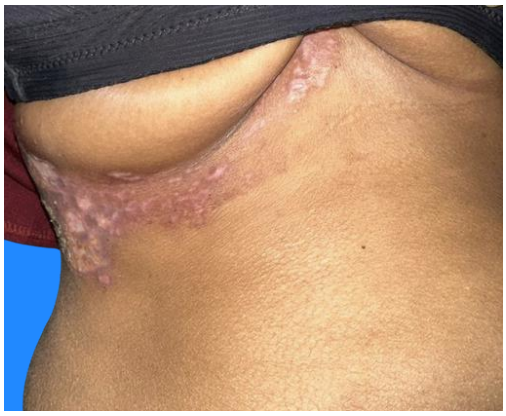


Figure 2. Dermatological status on day one of patient visit. Multiple clustered vesicles on an erythematous macule with normal skin between clusters distributed within dermatomal T5-T7.

DISCUSSION

Varicella zoster virus (VZV) infection has two forms of manifestation, varicella and herpes zoster. On its primary infection, it will emerge as acute varicella or chickenpox commonly occurs during childhood, and after recovery, the virus will be dormant in the dorsal root of the ganglion. Once the immunity of the host decreases it could trigger the reactivation of VZV and form herpes zoster manifestation. Reactivations occur due to decreased immunity of the host, especially the cellular mediated immunity (CMI).(van Oorschot et al., 2021) Cellular-mediated immunity holds an important aspect in the inactivation of herpes zoster.(Koshy et al., 2018)



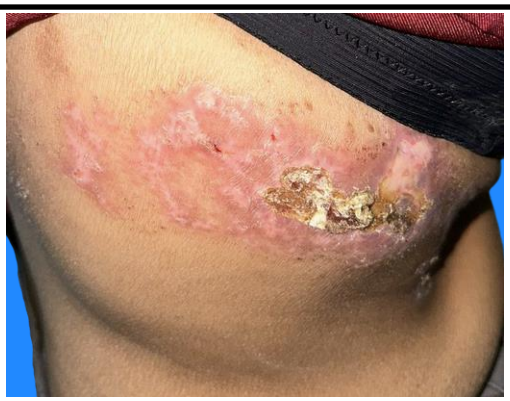


Figure 3. Dermatological status 14 days after acyclovir treatment. Multiple ulcers with yellow-brownish-colored crusts.

Decreasing CMI might be related to age-related decreasing immunity or immune-senescence and immunosuppressed condition.(van Oorschot et al., 2021) Considering the significance of age as a risk factor, the increasing life expectancy in the general population may considerably increase HZ annual cases and disease burden.(van Oorschot et al., 2021)

Herpes zoster infection has several risk factors such as gender, ethnicity, family history, and comorbidities such as systemic lupus erythematosus, asthma, diabetes mellitus, and chronic obstructive pulmonary disease, and immunocompromised condition both due to disease and therapy, such as a patient who receiving immunosuppressant agent and chemotherapy agent.(Koshy et al., 2018; van Oorschot et al., 2021) Person with malignancy also has a higher predilection for the prevalence of herpes zoster infection. A study stated that the hematological cancer population has a higher risk of herpes zoster infection than solid organ cancer.(Koshy et al., 2018) In our patient the immunocompromised condition was caused by hematological cancer, multiple myeloma stage III, and the consumption of chemotherapy agent, bortezomib.

Multiple myeloma is the second most common type of hematological cancer. It is characterized by the accumulation of malignant plasma cells in the bone marrow, leading to hypercalcemia, bone destruction, anemia, and renal failure.(Díaz-Tejedor et al., 2021) Bone marrow microenvironment is constituted by different components including immune cells (T cells, natural killer cells, dendritic cells, etc), non-immune cells (bone marrow stromal cells, osteoblast, osteoclast, etc), matrix protein, and secreted soluble factors

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(cytokines, growth factors, etc). In multiple myeloma patients, the production of bone marrow will be suppressed, including the production of immune cells, hence it will alter the number and the function of immune cells, causing an immunocompromised condition.(Díaz-Tejedor et al., 2021) Renal impairment was also found in our patient.

Antiviral is the pivotal management in herpes zoster, there are acyclovir, valacyclovir, and famciclovir. Early administration of antiviral helps in reducing the pain, promotes fast healing, and prevents post-herpetic neuralgia. Acyclovir and valacyclovir are thought to be less commonly caused acute kidney injury compared with famciclovir.(Koshy et al., 2018) Acyclovir is the most prescribed antiviral of VZV, this substance is excreted through renal. Even though it is a well-tolerated medication, there were several reports of acyclovir-induced severe nephrotoxicity, especially in intravenous acyclovir.(Koshy et al., 2018; Yildiz et al., 2013) Acyclovir-induced renal failure could happen in 12-48% of cases. It is characterized by a decrease in renal function within 12-48 hours of drug administration, indicated by a rapid rise in serum creatinine and abnormal urine sediment.(Yildiz et al., 2013)

Several pathomechanisms might explain the occurrence of acyclovir-induced acute kidney injury, the formation of crystal nephropathy that obstructs the renal tubules, acute interstitial nephritis (AIN), and acute tubular necrosis (ATN).(Fleischer & Johnson, 2010) Obstruction of the renal tubules will eventually resist the renal blood flow hence increasing the level of serum creatinine. Several risk factors increase the possibility of acyclovir-induced acute kidney injury such as hypovolemia, rapid intravenous infusion, history of acute kidney injury before, excess medication dosage concerning renal function, and concurrent use of other nephrotoxic agents.(Fleischer & Johnson, 2010) In this case, where there was an increasing renal function test we must consider the possibility of toxicity of acyclovir, even though this patient didn't have any risk factor for the formation of acyclovir crystal nephropathy. If renal toxicity develops, physicians need to stop the antiviral administration and proceed with supportive management including rapid hydration.(Htwe et al., 2008) When physicians encounter an acyclovir-induced renal toxicity several management options can be considered. A study has reported the possibility of using famciclovir as the substitute in a case with acyclovir-induced renal toxicity.(Htwe et al., 2008)

Valacyclovir is the prodrug of acyclovir that has a better absorbability and higher level of bioavailability than acyclovir, with three to fivefold higher bioavailability.(Achar et al., 2011; Rajalakshmi et al., 2010) Thus reducing the daily dosing and ensuring better compliance.(Achar et al., 2011) Both valacyclovir and acyclovir have the same safety profile.(Beutner et al., 1995) Acyclovir's safety profile has already been reported for more than 18 years and has well-documented efficacy for speedy rash healing and decreasing the pain of herpes zoster.(Achar et al., 2011) In this case, acyclovir with a renal-adjusted dose was chosen rather than valacyclovir because of acyclovir's history of safety profile, efficacy, better cost-effectiveness, and it is widely available in our health care facility.

Since valacyclovir is a prodrug of acyclovir there is no advantage in using valacyclovir in acyclovir-induced renal toxicity.(Htwe et al., 2008)

Renal dose adjustment is needed to be considered in patients with herpes zoster that need acyclovir treatment. Patient with underlying renal impairment and hypovolemia/ volume depletion, the administration of bolus intravenous acyclovir might lead to reversible acute renal failure in approximately 5% of patients.(Htwe et al., 2008) Acyclovir dose needs to be reduced based on the e-GFR.(Ashley et al., 2019) e-GFR was calculated with the Cockcroft-Gaulft formula, and we found the e-GFR was 17ml/mins which represents a decreasing glomerular filtration rate. That's why we reduced acyclovir dosage to 800 mg three times daily. Paracetamol was chosen to control the pain in this patient rather than give a non-steroidal anti-inflammatory drug which can lead to nephrotoxicity in this patient.

Table 1. Renal dose adjustment for acyclovir(Ashley et al., 2019)

e-GFR (ml/mins)	Acyclovir
25-50	Dose as in normal renal function
10-25	Simplex:200mg 3-4times daily Zoster: 800mg 8-12 hours
<10	Simplex: 200mg every 12 hours Zoster: 400-800mg every 12 hours

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Vaccination for VZV currently becomes the mainstay prevention effort to reduce the relapse episode of herpes zoster.(Koshy et al., 2018) Currently, two vaccinations are available for VZV, live attenuated VZV vaccine (Zostavax) and recombinant, adjuvanted VZV glycoprotein E subunit vaccine (Shingrix).(Patil et al., 2022) Live attenuated VZV vaccine is prohibited for immunocompromised persons. Zoster vaccine recombinant, adjuvanted is a two-dose vaccine containing glycoprotein E combination with adjuvant ($AS01_B$), that is already licensed by the Food and Drug Authority (FDA) in use for immunocompetent adults aged ≥50 years old or immunocompromised adults aged ≥18 years old. Immunocompromised adults need earlier administration of zoster vaccination due to the higher risk of complications in this population. This recombinant vaccine has a high efficacy and acceptable safety profile, it has the potential to prevent the incidence of herpes zoster and related complications. The vaccine efficacy (VE) profile has been reported in several studies, with VE 87.2% (44.3% - 98.6%) for hematologic malignancies.(Anderson et al., 2022) The lifetime risk of the unvaccinated population ranged between 20-30%.(van Oorschot et al., 2021) Immunocompromised status is an important risk of herpes zoster recurrence including hematologic malignancy.(Parikh et al., 2024). Therefore, because this patient has a high probability of recurrence episode of herpes zoster, this patient was educated to get herpes zoster vaccine to prevent the recurrence of herpes zoster.

CONCLUSION

Herpes zoster infection is more commonly reported in immunocompromised populations and could accompanied by more severe clinical manifestations, complications, and the possibility of recurrence. Multiple myeloma is commonly accompanied by renal impairment, hence in a population with immunocompromised, we need to be aware of other potential comorbid. The consideration for renal dose adjustment is very important to prevent the possibility of renal toxicity and maintain drug efficacy.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

HK, ANH: Conceptualization, writing original draft preparation. HM, TI, MDA, LA, ANH: supervision and review.

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