CASE REPORT

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Herpes Zoster on a bladder cancer patient - a rare case

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ABSTRACT

Introduction: Herpes zoster (HZ) is caused by reactivation of latent varicella-zoster virus (VZV) infection due to disturbance in T-cell mediated immunity. Risk factors include malignancy and therapy related to malignancy. Bladder cancer has a moderate association with HZ, with a risk increment of 10-50%. The rate of HZ in bladder cancer patients is 8/1000.
Case description: A 57-years-old man with bladder cancer T4bN3M0 complained of a painful erythematous vesicular rash on the left front abdomen extended to the back 1 week prior, accompanied by fever and burning sensation. He has had regular chemotherapy using Gemcitabine and Cisplatin, and radiotherapy with 2 Gray doses each session. Dermatological examination showed multiple well-defined erythematous-based vesicles, clustered on the left abdominal, flank, and posterior thorax region at T7-T9 dermatome. Tzanck-smear examination showed multinucleated giant cells. The patient was given acyclovir, paracetamol, and wet dressing on vesicles. His chemoradiotherapy was also halted. On the 7th day of evaluation, there were no new lesions and his complaints improved. In cancer patients, CD4+ and CD8+ levels decreased, accompanied by lymphocyte proliferation impairment. Cytotoxic chemotherapy agents work by attacking proliferation cells, affecting immune-related cells. Ion radiation in radiotherapy interferes with a regional cellular immune response that inhibits viral reactivation.
Conclusion: Principal HZ management in cancer patients includes antiviral and analgesics. In cancer patients, the occurrence of HZ can disturb and postpone management related to malignancy. The postponement of chemoradiotherapy is based on the patient's conditions and the severity of the disease.

Keywords: herpes zoster, bladder cancer, chemotherapy, radiotherapy.
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INTRODUCTION

Varicella-Zoster Virus (VZV) infection is an opportunistic infection that often occurs in immunocompromised patients. This infection occurs due to the reactivation of asymptomatic latent infections and often occurs in herpes family viruses, such as Herpes Simplex Virus (HSV) and VZV.[1] The reinfection of VZV, commonly called Herpes Zoster (HZ), occurs due to a disturbance in the cellular immune response. Herpes Zoster occurs in 20-30% of individuals, about 3-5 per 1,000 people per year.[2] It can cause a variety of complications that can interfere with the quality of life, such as involvement of ophthalmic nerves, postherpetic neuralgia, and other complications.[3]

Herpes Zoster can occur in immunocompetent patients, but immunocompromised conditions increase the risk of HZ occurring. Risk factors that increase the incidence of HZ include old age, the presence of HIV infection or other infections, organ transplantation, malignancy, and therapy related to malignancy.[4] Immunocompromised patients have a higher risk of developing HZ, with more severe clinical symptoms, as well as having a higher risk of developing severe complications and postherpetic neuralgia.[2]

Malignancy and malignancy treatment cause immunosuppression conditions in patients thus increasing the risk of HZ. This condition may impair quality of life and disturb management related to malignancy. Therefore, a deeper understanding of HZ in patients with malignancy, factors that influence the occurrence of HZ in malignancy, as well as the management of HZ in malignancy, are needed. This case report discusses the occurrence of HZ in a 57-year-old man who is undergoing chemotherapy and radiotherapy for bladder cancer. There is little information on herpes zoster infection in bladder cancer patients as a complication during adjuvant chemoradiotherapy. The rates of HZ and HZ-related complications are significantly higher for hematologic than solid cancer patients. Bladder cancer has a moderate association with HZ, with a risk increment of 10-50%. The rate of HZ in bladder cancer patients is 8/1000.[4]

CASE DESCRIPTION

A 57-year-old man was consulted from Urology Department to the Dermatology and Venerology Department of Dr. Saiful Anwar Malang General Hospital with complaints of an erythematous vesicular rash on the left front abdomen area to

the back 1 week prior. Initially, there were just a few vesicles on the left side of the abdomen, then the lesion multiplied and spread to the flank and back. Gradually the vesicles deflated then dried up and became reddish. Complaint accompanied by burning sensation with VAS 6/10. There was no itch complained. Two days before the vesicles appeared, the patient experienced fever. There was no cough, coryza, nausea, and vomiting.

The patient was diagnosed with bladder cancer T4bN3M0. The patient refused to undergo surgery so he was given radiotherapy as his treatment. To increase the sensitivity of the radiotherapy, the patient was also given chemotherapy. The patient had undergone chemoradiotherapy for 4 months. The chemotherapy was conducted with Gemcitabine 1% and Cisplatin regiment repeated every 21 days and planned for 6 series. Radiotherapy was planned 33 times, 2 Gray was given for each session. The patient last underwent therapy 1 week ago, 2 days before the complaint appeared.

There were no similar complaints before. The patient did not remember whether he had chickenpox or not. No patient's family has experienced similar complaints. The patient had never given ointment and denies applying oils such as eucalyptus oil or wasp oil in the complaint area.

General examination showed that patient was compos mentis, his GCS was 456, moderately ill. His blood pressure was 130/70 mmHg, his heart rate was 84 times per minute, his respiratory rate was 18 times per minute, and his body temperature was 36,9°C. Physical examination on the thorax and abdomen region was within normal limits. There was no edema on his extremities and his acral was warm. No enlargement of the lymph nodes is observed.

Dermatological examination of the left abdominal region, flank, and posterior thorax (Figure 1) following the dermatome T7-T9 sinistra, showed multiple well-defined erythematous-based vesicles, clustered, sagging walls, with varied shape and size. There were multiple well-defined erosion and brownish crusts, that varied in shape and size.

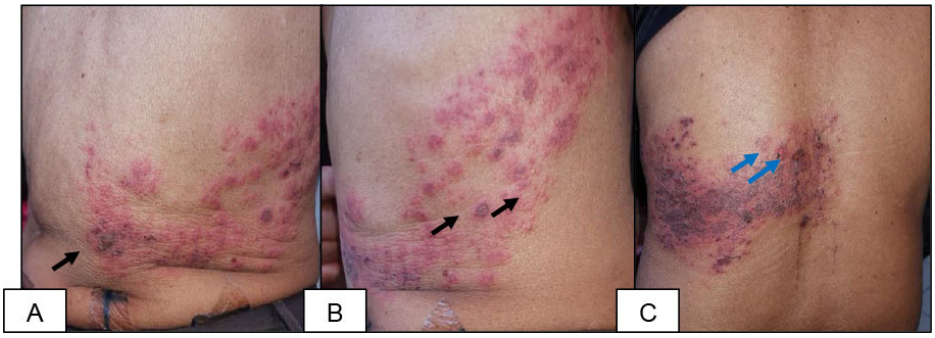

Figure 1. Dermatological examination on the left abdomen (A), flank (B), and posterior thorax (C) region. Multiple well-defined erythematous-based vesicles, some were clustered (✇), erosion (✇), and brownish crusts.

Tzanck smear examination of vesicles in the abdominal region showed the presence of multinucleated giant cells. Complete peripheral blood examination result was within normal limit. Leucocyte count showed neutrophilia (82,2%) and lymphopenia (9,7%). Liver marker examination was within the normal limit, there were a slight increase of ureum (50,4 mg/dL) and creatinine (1,3 mg/dL) in renal marker examination.

Based on anamnesis, physical examination, and additional examination, the patient was diagnosed with herpes zoster thoracoabdominal sinistra and was given acyclovir 5 x 800 mg per oral (po) for 7 days, paracetamol 3 x 500 mg po, and wet dressing on vesicles using saline solution 3 x 10 minutes as therapy. The patient was educated to delay and temporarily halt chemoradiotherapy treatment for his bladder cancer.

Evaluation on day seven showed good results. The patient's condition improved. The vesicles had dried up and some had become scabs. Reddish patches became brownish. There were still a few wounds. No new vesicles appeared. The patient did not complain of pain or itching. Dermatological examination of the left abdominal region, flank, and posterior thorax (Figure 2) showed multiple well-defined hyperpigmented patches, and irregular edges, that varied in shape and size. There was also multiple erythematous-based erosion, some were covered with brownish crusts, that varied in shape and size. Acyclovir therapy was discontinued. Gentamycin zalf was given 2 times a day, and applied on erosions. The patient was also educated about the risk of developing postherpetic neuralgia and to temporarily postpone his chemoradiotherapy until the lesion resolved completely.

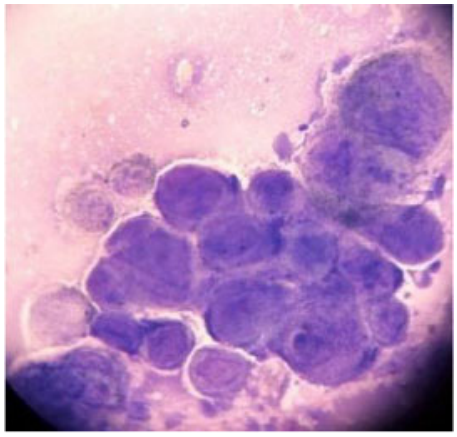

Figure 2. Tzanck smear examination from vesicles. Multinucleated giant cell (+).

DISCUSSION

Herpes Zoster (HZ) or shingles is a neurocutaneous disease that occurs due to the reactivation of latent varicella-zoster virus (VZV) infection from its dormant condition.[5,6] Herpes Zoster incidents increase from year to year. HZ incidents in the Americas, Europe, and Asia range from 3 to 5 per 100.000 people.[5] A total of 30% of the population is estimated to experience HZ, and at the age of 85 years, it is obtained that 50% of the population experiences HZ. The incidence of HZ in people aged 20-50 is 2.5 per 1,000 people, at the age of 60 it increases to 7 per 1,000 people. It is estimated that there are at least

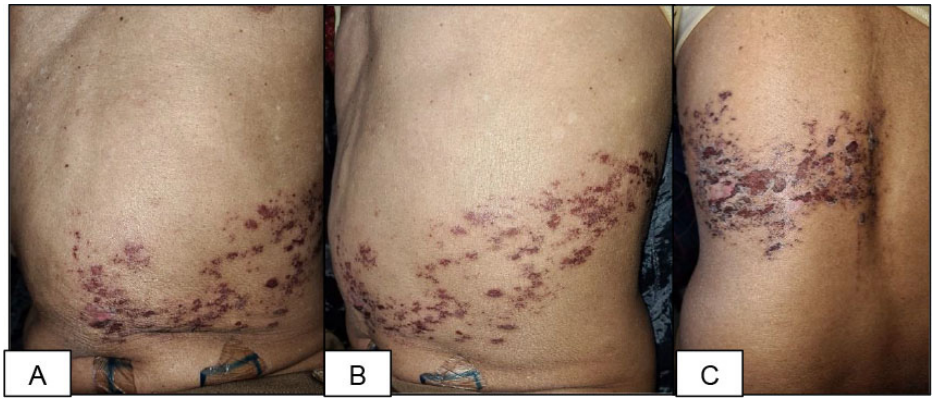

Figure 3. Dermatological examination follow-up on day-7. There were multiple hyperpigmentation patches, erosion, and brownish crusts on the left abdomen (A), flank (B), and posterior thorax region (C).

1.5 million new HZ cases in America each year, more than half of which occur in patients over the age of 60. A total of 90% of sufferers will experience pain, and a total of 5-30% of sufferers will experience postherpetic neuralgia.[5,7,8] There is no difference in incidents between males and females.

Varicella-Zoster Virus reactivation is thought to be influenced by T-cell-mediated immunity disorders. After a primary infection, the virus can latently infect cranial and dorsal ganglia neurons. Once VZV reaches neuron bodies, effector lymphocyte cells, CD8+ and CD4+ will maintain viral latency at cranial and dorsal root ganglion, sensory neuron cell bodies, and autonomous tissues. Varicella-Zoster Virus reactivation is inhibited by the immune system mediated by the cytolytic effects of CD8+ T lymphocyte cells through the production of IFN-γ, and by CD4+ which triggers cytokine secretions of TNF-α, IFN-γ, IL-2, as well as memory B cell stimulation and IgG-mediated B cell proliferation. Interleukin-2 will trigger CD8+ to secrete proteases, IFN-γ, and lysines which will destroy infected cells.[9] In addition, Nerve Growth Factor (NGF) also maintains latency by activating mTORC-1, which will phosphorylate the translation of 4E- binding protein 1 (4E-BP) translation factors. 4E-BP is a translation repressor that activates dependent-cap mRNA translation, which inhibits virus reactivation.[7]

The virus will be activated if lymphocyte T cells level decrease, such as in immunocompromised conditions e.g., old age, the presence of HIV infection or other infections, organ transplantation, malignancy, and therapy related to malignancy.[4] Cellular stress activates the virus by triggering DNA and viral replication. Replication of VZV viruses lasts up to 5 days. Virus components are transported along the nerves through the body of neurons. Epithelial transport through glycoproteins E and I cause the virus to replicate in the epithelium and spread rapidly to epithelial cells through tight junction.[7]

One of the risk factors that trigger VZV reactivation is malignancy. A study showed that the presence of malignancy triggered the occurrence of HZ, in which of the 192,081 patients diagnosed with HZ, a total of 16,219 (8.4%) have a history of malignancy.[5] The strongest association is obtained between hematological malignancy and HZ in the first year after diagnosis. The risk of HZ in solid organ cancer is also high, but this risk decreases in the 3 years after diagnosis. Solid-organ cancers that have the strongest association with HZ are central nervous system cancers, followed by lung cancer, as well as oral and esophageal. Gastric, colorectal, breast, ovarian, prostate, renal, and bladder cancers are cancers that have a moderate association with HZ, with an increased risk of HZ of about 10-50%.[5] The increased risk of HZ occurrence in malignancy is likely caused by a decrease in cell-mediated immunity. In patients with malignancy, CD4+ and CD8+ levels decreased, accompanied by lymphocyte proliferation impairment.[9]

In patients with solid organ cancer, the risk of developing HZ increased significantly in patients undergoing chemotherapy compared to those who did not undergo chemotherapy. A study showed the risk of VZV infection increased 13-fold in breast cancer patients undergoing chemotherapy.[4] Another study conducted by Choi, et al, reported the incidence of HZ in non-small cell lung cancer (NSCLC) patients who underwent chemotherapy amounting to 1.54% of the population.[10] The incidence of HZ is known to be higher in patients undergoing chemotherapy using cytotoxic regimens such as gemcitabine, carboplatin, cisplatin, docetaxel, paclitaxel, vinorelbine, and etoposide, with the highest incidence occurring in the use of taxane-based chemotherapy (paclitaxel, docetaxel) due to its strong immunosuppressive properties.

In addition, there is an increase in HZ incidence in malignancy patients undergoing radiotherapy. Shimizuguchi's study reported that of the 17,655 malignancy patients, 294 had HZ and 123 of them had HZ after undergoing chemotherapy.[3] When compared to patients who only undergo chemotherapy, the risk of HZ is higher in patients undergoing chemotherapy and radiotherapy. HZ usually occurs in 3-6 months after radiotherapy. VZV infection is significantly high in the first 5 months after undergoing radiotherapy. A total of 3.7% of patients with breast cancer had HZ in the first 2 years after radiotherapy. In addition, 8.1% of lung cancer patients had HZ within the first year after radiotherapy began. Yo-Liang Lai et al. research reported 12,45 HZ incidents per 10,000 people per year in breast cancer patients undergoing radiotherapy, with 3.85 times increased risk in patients over the age of 65. Compared to a healthy person (0.25-0.35%), the incidence of HZ was higher (3.7%) in breast cancer patients undergoing irradiation therapy with doses of 44-58 Gy, in a fraction of 1.8-2 Gy.[4]

VZV reactivation in chemotherapy and radiotherapy can be caused by disruption of the local and systemic immune systems. Cytotoxic chemotherapy agents work by attacking proliferation cells, affecting epithelial cells, immune-related cells, and hematopoietic cells, causing disorders of the cutaneous, hematological, and immune

systems. Radiotherapy can cause local immune system disorders. The presence of local trauma to the skin can increase the occurrence of HZ. In radiotherapy, ion radiation interferes with the regional cellular immune response that plays a role in the inhibition of viral reactivation. Radiation can damage cellular immune components in the radiated area. Radiation is known to interfere with lymphocyte function. A high dose of radiotherapy accompanied by chemotherapy weakens the local and systemic immune system, thus triggering VZV reactivation.[3,4]

In this case, the 57-year-old patient has bladder cancer T4bN3M0 and was undergoing chemotherapy and radiotherapy in the past 4 months using Gemcitabine 1% and Cisplatin repeated every 21 days for 6 series, and radiotherapy for 33 times, each dose was 2 Gy. Risk factors for HZ in this patient were the patient's age, bladder cancer, as well as chemotherapy, and radiotherapy. Bladder cancer is known to be cancer that moderately triggers VZV reactivation. The combination of chemotherapy and radiotherapy could be the main factor that triggered the occurrence of HZ in this patient. Another factor is the chemotherapy regimen used by a patient. The patient was given Gemcitabine and Cisplatin regimens, which are known to be cytotoxic chemotherapy regimens. This regimen can weaken the immune system response mediated by T lymphocytes due to its cytotoxic effects, which can influence HZ reactivation. The patient also underwent radiotherapy with a dose of 2 Gy, similar to the research conducted by Yo-Liang Lai. The combination of chemotherapy and radiotherapy is known to decrease the local and systemic immune response, which triggers the onset of HZ.

Herpes Zoster symptoms begin with paresthesia and pain in the dermatome area, 1 to 3 days before a skin lesion appeared. The infected area will experience abnormal sensations such as itching, tingling, burning, and sharp pain. Pain is usually sedentary and accompanied by hyperesthesia of the skin according to the dermatome. These symptoms are common in patients aged 60 years and over.[8] Localization and distribution of the lesion are the characteristics of HZ lesion, including unilateral limited to skin innervated by single sensory neuron ganglia, such as an ophthalmic branch of the trigeminal nerve, or T3 to L2 branch of the spinal cord. The most frequently affected areas are the trunk (33.6%), chest (26%), flank (14.1%), and face-neck (11.9%)1. Herpes Zoster lesions commonly appear as clustering erythematous-based vesicles, initially appearing as erythematous macules and papules according to dermatomal distribution. Vesicles will appear within 12 to 24 hours after the first lesion and will turn into pustules in 3 days. Pustules will then dry out and become crusty within 7 to 10 days and last up to 2 to 3 weeks. Lesions will last longer in older people.[8]

Herpes Zoster management can be done in an outpatient setting. The treatment is carried out to reduce the severity and duration of pain, trigger the healing of skin lesions, prevent the formation of new skin lesions, lower the risk of transmission, and prevent postherpetic neuralgia. Herpes Zoster management consist of antivirals and analgesics.[11] Nucleoside analogs such as acyclovir, valacyclovir, and famciclovir can be given. Acyclovir 5 x 800 mg po, or valacyclovir 1 gram po, or famciclovir 3 x 500 mg po for at least 7 days or until the lesions dry can be given.[1] Guanosine analog, acyclovir, is the first line treatment for HZ. Acyclovir has optimal bioavailability and is available in topical, oral, and intravenous dosage forms.[7] Oral antiviral can be administered within 72 hours after the onset of lesions. In immunocompromised patients, antiviral should be administered immediately after the onset of lesions. In severely immunocompromised patients, intravenous antiviral (acyclovir 10 mg/kg/for every 8 hours) can be administered to delay disease progression and decrease the duration of viral replication. Topical antiviral doesn't have any significant effect, so it is not recommended. In cancer patients who undergo radiotherapy, the radiotherapy cycle may be suspended or the dose lowered depending on the degree of severity.[11]

In HZ patients, analgesics should be administered in conjunction with antiviral to control pain and prevent postherpetic neuralgia. The analgesics given can be adjusted to the patient's pain VAS. Acetaminophen can be given for mild to moderate pain management. For more severe pain, weak opioids or tramadol may be given. If the symptoms don't improve, stronger opioids, such as morphine, accompanied by lidocaine patches can have a positive effect. In addition, anticonvulsant and tricyclic antidepressant drugs can also be administered as a combination therapy in patients with moderate to severe VAS pain. Oral corticosteroids can be given to immunocompetent patients without contraindications to support pain management. Corticosteroids are administered as soon as the diagnosis is upheld as an anti-inflammatory on the dorsal ganglion radix. Patients should be educated to maintain personal hygiene, especially in hands and lesions, keep the lesion area clean and dry, and use antibacterial soap to prevent the occurrence of bacterial superinfection in lesions.[11]

In this case, despite being in an immunocompromised condition, the patient's condition, in general, was good so he was given acyclovir 5 x 800 mg po for 7 days. Pain experienced by the patient was moderate pain therefore paracetamol was given. Wet dressing using saline solution 3 x 10 minutes applied to vesicle lesions. The patient was educated to delay and temporarily halt chemotherapy treatment for his bladder cancer. Chemotherapy and radiotherapy may be postponed at the doctor's policy by assessing the condition and severity of the symptoms experienced by the patient.[7,11,12] Although the patient's condition was generally good, if there were conditions such as disseminated HZ, or HZ complications such as ophthalmic HZ, chemotherapy and radiotherapy should be postponed temporarily, or continued with a lowered dose.

On the 7th day of evaluation, the patient's complaints were improved and no new lesions were found. The antiviral was discontinued. Paracetamol can be continued if there is still pain. Gentamycin zalf was given to erosion areas to prevent bacterial infection of the lesion. Chemotherapy and radiotherapy can be continued if the lesion has been resolved completely and the patient has no symptoms.

STRENGTH AND LIMITATION

The strength of this case report is it was conducted in an integrated hospital, and because of that, the patient was easily monitored during the treatment. Besides that, the financing was also used by health insurance so that treatment was not hampered.

For the limitation, it was difficult to contact the patient after he got the treatment for his Herpes Zoster, so we cannot determine the prognostic of bladder cancer histologically after herpes zoster infection. The medical records were still not well recorded so it is difficult to follow up.

CONCLUSION

Principal HZ management in cancer patients includes antiviral and analgesics. In cancer patients, the occurrence of HZ can disturb and postpone management related to malignancy. The postponement of chemoradiotherapy is based on the patient's conditions and the severity of the disease.

DISCLOSURES

Funding

No funding.

Conflict of Interest

The authors declare no conflict of interest.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report.

Author Contribution

Dhelya Widasmara and Santosa Basuki were involved in the conception and supervising of the manuscript. Besut Daryanto and Kurnia Penta Seputra were involved in supervising the manuscript. All authors prepare the manuscript and agree for this final version of the manuscript to be submitted to this journal.

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