Herpes Zoster in a Patient with History of Breast Cancer: A Case Report

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INTRODUCTION

Herpes zoster (HZ) is a disease caused by reactivation of latent varicella-zoster virus (VZV). Immunodeficiency, such as malignancy, is one of the causative factors of HZ. Clinically HZ manifests as erythematous macules within 12-24 hours, then develops into unilateral clustered vesicles that usually do not cross the body's midline and are confined to areas of the skin innervated by a sensory ganglion. Tzanck test is a standard diagnostic tool for diagnosing HZ, as it can detect multinucleated giant cells.

A 57-year-old woman presented to the outpatient dermatology and venereology clinic of Dr. Moewardi General Hospital, painful, easily ruptured vesicles on her left chest spreading to her back, left armpit and arm. She was diagnosed with breast cancer five years ago. She had completed her cancer therapy, and in November 2020, she had a total mastectomy of her right breast. Physical examination obtained multiple unilaterally clustered vesicles, which were partially crushed on an erythematous base with some erosive areas in a C6 and T4 dermatomal distribution on the left side. Tzanck examination showed multinucleated giant cells. She was treated with aciclovir tablets 800 mg/4.5 hours for ten days, gabapentin tablets 300 mg/24 hours for three days and then every 12 hours from day 4 to day 7, Neurosanbe® tablets/8 hours, wound care with 0.9% NaCl compression for 10 minutes every morning and evening, and mupirocin ointment 2% applied on the erosive area as well as salicyl t alc on the unburst vesicles. Immunosuppressive conditions such as malignancies result in reduced cell-mediated immunity (CMI), which increases the risk of viral infections such as herpes zoster. Commonly people with malignancies have low CD4+ and CD8+ cell counts and reduced lymphocyte proliferation. All the above conditions can be risk factors for the development of HZ.
infections may increase after postoperative radiotherapy (3-5 times) suggesting an immunosuppressive association of radiation treatment with disease. A retrospective study by Darvishi and Veseli reported the frequency of zoster has been reported to be 4% in the first 2 years after completion of radiotherapy. Cancer patients with radiation therapy can have a severe disease course compared to healthy adults and is related to host immunity. Adjuvant chemotherapy may facilitate reactivation of herpes infection, suggesting that shingles may present in immunosuppressed patients.7

Herpes zoster is characterised by prodromal symptoms of low-grade fever, headache, or malaise (1-5 days). Pain may occur one or more days before the onset of the skin eruption.5 Clinical manifestations of HZ generally begin with erythematous macules in the first 12-24 hours which then develop into clustered, unilateral vesicles that do not cross the midline of the body and are limited to the skin area innervated by one sensory ganglion. The trigeminal cranial nerve, cervical sensory nerve and thoracic sensory nerve are the sites involved. Herpetiform vesicles may appear in clusters on an erythematous base with segmental arrangement. Burning, stabbing, or itching pain accompanied by clustered vesicles on specific body parts associated with one or more skin dermatomes occurs in approximately 70-80% of cases.8 The differential diagnosis of HZ is herpes infection.

The differential diagnosis of HZ is herpes simplex zosteriformis infection, contact dermatitis, insect bites and burns.7 The diagnosis of HZ can be made clinically based on the characteristics of a diffuse or unilateral dermatomal vesicular rash.10 Supporting examinations that can help confirm the diagnosis of HZ include Tzanck examination where multinucleated giant cells will be found, while the gold standard of diagnosis in HZ is by Polymerase Chain Reaction (PCR).11,12

Herpes zoster can develop into more severe conditions such as encephalitis, ophthalmic HZ, Ramsay-Hunt syndrome, and post-herpetic neuralgia (NPH).13 Management in HZ is in the form of antiviral therapy, analgesic, or symptomatic and topical therapy.11,12 In immunocompromised patients, the main antiviral therapy is acyclovir at a dose of 5x800 mg for 10 days. Valacyclovir (Valtrex®), another drug which is a prodrug of Acyclovir can be given at a dose of 3x1000 mg for 10 days and Famciclovir is taken 3x500 mg daily for 10 days. All three drugs can accelerate the duration of rash healing and reduce the severity of acute pain in the elderly if given within 72 hours of rash onset.

This paper will discuss one case report of Herpes zoster cervical 6 to thoracic 4 (C6-T4) sinistra in a breast cancer patient post total mastectomy dextra. The purpose of writing this paper is to increase knowledge as a dermatologist regarding the clinical picture, risk factors, therapy, complications that can occur in HZ and its relationship with malignancy, as well as the management of HZ in patients with comorbidities, so as to provide better treatment.

METHODS

Patient Mrs K, 57 years old, residing in Banjarsari, Surakarta, was referred by the surgical oncology department to the Skin and Genital Polyclinic of Dr Moewardi Hospital, Surakarta with complaints of ruptured clear fluid-filled pustules and burning pain on the left chest then spread to the back, armpit, and left arm. The results of autoanamnesis on the history of the current disease, appeared clear fluid-filled pustules on the left chest that spread to the back, armpit, and left arm since 3 days ago. The patient treated by applying body lotion and olive oil, but the complaints did not decrease and increased itching accompanied by pain and fever.

The patient has a history of dextra breast cancer since 5 years ago and has undergone total dextra mastectomy in November 2020, currently the patient is routinely controlled in the oncology surgery department and is given Arimidex® tablets 1 mg once a day. The patient has no previous history of similar illness and has no known history of varicella with a complete immunisation history. The patient has no history of allergies, diabetes, high blood pressure and no family members who suffer from skin diseases like the patient.
On physical examination, vital signs were within normal limits, body weight 38 kg and pain score 3. Dermatological status in the superior extremity region et axillaris et truncus anterior et posterior sinistra appeared unilateral clustered multiple vesicles with a partially broken erythema base forming crusts as high as cervical dermatome 6 to thoracic 4 (C6-T4) sinistra (Figure 1). The results of the history and physical examination of the differential diagnosis in this case are HZ as high as dermatome C6-T4 sinistra with breast cancer after total mastectomy dextra, irritant contact dermatitis with breast cancer after total mastectomy dextra, and dermatitis venenata with breast cancer after total mastectomy dextra.

The results of Tzanck’s examination taken from the vesicle lesion on the left chest area showed multinucleated giant cells (Figure 2). Based on the results of history, physical examination and laboratory examination, the patient was diagnosed with HZ as high as dermatome C6-T4 sinistra in breast cancer patients after total mastectomy dextra.

The management in this patient included the administration of acyclovir tablets 800 mg every 4.5 hours orally for 10 days, gabapentin tablets 300 mg every 24 hours orally for 3 days and continued 300 mg every 12 hours on day 4 to day 7, neurosanbe® tablets every 8 hours orally, wound care with NaCl 0.9% compress for 10 minutes every morning and evening and then apply mupirocin ointment 2% on the erosion area and on the unbroken vesicles given salicyl powder.

Figure 2. Tzanck’s examination: multinucleated giant cell (orange arrow) [Giemsa, 10x].

RESULTS AND DISCUSSION

Herpes zoster is a viral disease caused by reactivation of previously dormant varicella-zoster virus (VVZ) in the sensory ganglia of the cranial nerves or dorsal radial ganglia following previous varicella infection. The highest age group affected by Herpes zoster is 45-64 years old at 73% and HZ is more common in men (54.5%) than women (45.5%). The individual risk of developing HZ is 30%.14 The incidence of HZ in populations in the United States, Canada, South America, Europe, Asia, Australia varies between 4-4.5 per 1,000 people per year.15

Varicella-zoster virus enters the body through the respiratory tract and spreads rapidly from pharyngeal lymphoid tissue to T lymphocytes. The immune response to VVZ infection consists of three components, namely innate immunity mediated by IFN-α, humoral immunity and cell-mediated immunity (CMI). The latter is an important component of the host response as VZV is a cell-associated virus and T-cell mediated immunity is required to eliminate intracellular pathogens. All herpesviruses can establish latency. Two hypotheses have been proposed to explain how VZV becomes latent in dorsal radial ganglia and cranial radial ganglia: the first hypothesis is that VZV is produced in the epidermis and infects intraepidermal sensory neurons. The virus then travels by retrogradational transport in the axon to reach the cell body, where latency is established. This theory is supported by the observation that the distribution of HZ reflects the relative distribution of varicella skin lesions. The second hypothesis is that the VVZ is carried to the dorsal radial ganglion or cranial radial ganglia within infected T cells during the viremia stage of varicella infection.

These infected T cells join the neuron and infect the neuronal cell body. The virus begins to proliferate within the neuron, but cell death is prevented, proliferation stops, and latency is established. Viral gene transcription products are required to maintain latency, but it is host factors that then determine whether the virus remains latent.16

Activated varicella-zoster virus is carried along microtubules in sensory axons to infect epithelial cells, usually without viremia. The resulting skin infection is a rash on a dermatome innervated by a single sensory nerve. The trigeminal (cranial nerve), cervical and thoracic sensory nerves are most involved in VVZ reactivation, but there is also inflammation and necrosis of all other cell types within the affected ganglion. Herpes zoster occurs when the VVZ reactivates from its dormant state during periods of decreased cell-mediated immunity (CMI), causing a characteristic rash and pain that can have a significant impact on quality of life. Risk factors for HZ are emotional stress, medication use (immunosuppression), comorbid conditions such as family history, female gender, HIV-AIDS or malignancy, age over 50 years, bone marrow or organ transplantation, trauma, and surgery.1,2,3,4,6

In general, people with malignancies have low CD4+ and CD8+ cells and impaired lymphocyte proliferation.2 The increased risk in older patients is likely due to immunosenescence, where the immune system progressively declines with age. In elderly patients with decreased immune function, VZV-specific T cell immunity (CD4, CD8, and memory T cells) is below the clinical threshold to maintain latent virus, thus increasing susceptibility to HZ. Patients with malignancies may experience immunosuppression mediated by cellular immune responses, and decreased immune responses may also result from chemotherapy, psychological stress, or physical trauma from surgery or radiotherapy, increasing the risk of HZ. Immunosuppressed conditions such as HIV/AIDS and malignancies lead to decreased CMI which increases the risk of viral infections, such as zoster. All of the above conditions can be risk factors for HZ.3,7

In our case, the 57-year-old patient had a history of breast cancer and had undergone treatment with radiotherapy, chemoradiotherapy and finally mastectomy on the dextra breast, which are factors that cause susceptibility to HZ. Increased age, female gender, white race, increased age, female gender, white race,
immunosuppression therapy and advanced stage are significant risk factors for HZ infection in cancer patients.\textsuperscript{17} Breast cancer is the most common cancer in women worldwide. It occurs in approximately 1.38 million new cases each year.\textsuperscript{18} In general, immunosuppression is one of the risk factors for HZ including patients with breast cancer. Immunocompromised condition in breast cancer patients can occur due to several mechanisms, the first is a defect in natural killer (NK) cells, patients with breast cancer tend to have low activity in several target cells. The second mechanism is the small number of cytokines produced by T lymphocytes. The third factor is the disruption of regulatory T cells, which are induced by the tumour causing a decline in the immune system.\textsuperscript{19} Patients diagnosed with cancer have an increased suspicion of HZ when early symptoms are present.\textsuperscript{19} The incidence of HZ is 3-5 times higher in breast cancer patients undergoing radiotherapy. The frequency of HZ was reported to be 4\% at 2 years post completion of the radiotherapy cycle. Radiotherapy affects lymphocyte function resulting in abnormal lymphocyte responses.\textsuperscript{20}

The incidence of Herpes zoster increases after radiotherapy especially in patients who are >65 years old and/or receiving chemotherapy. Cancer patients with radiotherapy may have severe reactions when exposed to HZ. Periodic clinical examination and additional serological examination in the first 5 months after radiotherapy is recommended to diagnose HZ early so that patients can receive immediate therapy and prevent serious complications.\textsuperscript{20}

The most frequent dermatomal involvement in HZ is in the thoracic dermatome. The clinical picture of HZ begins with prodromal symptoms in the form of pain, paresthesias and abnormal sensations such as superficial itching, tingling, burning, prickling according to the dermatome that denervates the affected sensory nerve ganglion 1-3 days sometimes a week or even longer before the skin rash appears. Pain may be persistent or intermittent. The lesion begins with the appearance of macular erythema, then papules form and within 12-24 hours develop into vesicles. The characteristic lesion in HZ is the presence of clustered vesicles on an erythematous base. These lesions occur unilaterally according to the dermatome area innervated by the infected nerve ganglion and do not cross the midline of the body. The lesions may affect a single dermatome or nearby dermatomes depending on the distribution of the sensory ganglion where the reactivation occurs. In individuals with HZ, new lesions may continue to appear until days 3-7. By day 3, the vesicles turn into pustules and then into crusts in 7-10 days and heal in 2-4 weeks. Prodromal symptoms may include fever, headache, malaise, and photophobia which may last for 1-5 days. In a study by Chen LK et al mentioned HZ in immunocompromised patients, but it is rare, usually involving two different dermatomes, can spread beyond the dermatomes and can involve internal organs.\textsuperscript{13,16}

In this case, the patient felt pain in the left chest area then spread to the back, armpit and left arm since 3 days before admission to the hospital accompanied by fever. The pain felt like burning in the chest, back, armpit and left arm and the patient said it sometimes felt itchy, then watery pustules appeared on the lesion area. The watery pustules were painful to the touch. Over the course of time, the watery pustules dried up into crust-covered erosions. The patient’s lesions are unilateral, and internal organ involvement due to herpes has not been evaluated.

The diagnosis of Herpes zoster can be made clinically by the onset of a characteristic skin eruption in the affected dermatome. However, the lesions may be atypical in immunocompromised patients so supporting investigations are required.\textsuperscript{8,21} The best diagnosis is made by Polymerase Chain Reaction (PCR) testing. A simple laboratory test is the Tzank test. Samples should be taken from new, intact, and uninfected lesions and ensure an adequate number of samples are examined. The cytological characteristics of herpes infection are acantholytic cells and datia cells with multiple nuclei (multinucleated giant cell). Tzank’s ability to detect acantholytic cells and multinucleated giant cells for viral infection is between 42\% and 90\%. In addition, the false positive and false negative rates are 3-13\% and 28\% respectively. Gram staining can be performed as an additional examination when secondary infection of skin lesions is suspected.\textsuperscript{22,23}

The differential diagnosis of this patient was irritant contact dermatitis and dermatitis venenata. Irritant contact dermatitis (DKI) is inflammation of the skin, resulting from a response to exposure to an irritant, physical or biological substance that contacts the skin without being mediated by an immunological process. In DKI, the first exposure to the irritant has been able to cause an irritating response in the skin that causes an inflammatory reaction in the form of

![Figure 3. A. The anterior trunkus region shows multiple vesicles clustered unilaterally with an erythematous base (red arrow) partially broken to form crusts (yellow arrow) B. Posterior trunkus region et mamae sinistra showing multiple vesicles with erythematous base (green)](image-url)
vasodilation and cell infiltration in the dermis and epidermis due to the release of proinflammatory cytokine IL-1 before skin damage occurs. In this case, there was a history of exposure and association with ingredients that may be weak irritants, namely body lotion and olive oil. But after the exposure was removed, the complaints did not improve and spread to follow the dermatome.

The next differential diagnosis in the patient was dermatitis venenata. Venenata dermatitis is caused by exposure to irritants such as pederin toxin, a toxin produced by paederus insects. The manifestation of dermatitis venenata is skin erythema accompanied by vesicles, pustules, or bullae that can become erosions that have a linear configuration. In addition, there is kissing lesion, where the lesion will appear on the opposite area to the previous lesion, such as the elbow or axilla. In this case, there was no known history of insect exposure, and the lesions matched the dermatomes.

The working diagnosis in this patient is Herpes zoster as high as dermatome C6-T4 sinistra with breast cancer after total mastectomy dextra. Based on anamnesis, complaints were obtained in the form of pain that felt like burning on the inside of the chest, back, armpit and left arm and the patient said it sometimes felt like itching, then watery pustules appeared on the arm area of the chest area and spread to the back, armpit, and left arm. The watery pustules were painful to the touch. The patient had a history of breast cancer with treatment of radiotherapy, chemotherapy and finally decided to mastectomy on the dextra breast. On dermatological examination of the superior limb region et axillary et trunkus anterior et posterior sinistra, multiple vesicles were seen unilaterally clustered with an erythema base partially broken to form crusts as high as cervical dermatome 6 to thoracic 4 (C6-T4) sinistra. Supporting examination has also been carried out on this patient, namely in the form of a tzanck examination with giemsa staining found the presence of multinucleated giant cells under a microscope.

Treatment of Shingles with antivirals and analgesics can reduce acute lesions and pain and prevent complications. Antiviral drugs have been shown to reduce acute pain, lesion severity and can accelerate lesion healing and reduce the duration of pain. The administration schedule and blood concentrations of the prodrugs valacyclovir and famciclovir are more constant than acyclovir. Paracetamol alone or in combination with weak opioids (e.g., codeine) is often used as analgesia.

Antiviral therapy is prescribed in patients >50 years of age, moderate or severe lesions, severe pain and in
immunocompromised conditions. Antivirals given 72 hours after lesion onset reduce the duration of viral replication, new lesion formation, severity, and duration of acute pain. Experts recommend starting therapy >72 hours after lesion onset if there is evidence of new lesion formation or if there is motor involvement, neurological and ocular complications. The dose of acyclovir given is 800 mg 5 times daily for 7–10 days, valacyclovir 1 gram per day for 7 days or famciclovir 500 mg every 8 hours for 7 days. Acyclovir, valacyclovir and famciclovir are guanine analogues that are phosphorylated by thymidine kinase to a triphosphate form that can inhibit VZV DNA polymerase. There is no difference between these three drugs in the end of treatment and have similar side effects. However, ease of dosing, drug availability, and cost need to be considered. There are several cases of acyclovir resistance in immunocompromised patients, so the possibility of resistance can be considered in Hz lesions that do not show a response to adequate drug administration.21 Acyclovir dose adjustment needs to be done in patients with chronic renal failure and it is necessary to calculate the glomerular filtration rate and creatinine clearance (CrCl) using the Cockcroft Gault formula or more precisely using 24-hour urine. Acyclovir dose adjustment, i.e., CrCl <25 mL/min: 800 mg 4-5 times a day, CrCl 10-25 mL/min: 800 mg every 8 hours, CrCl < 10 mL/min: 800 mg every 12 hours. Beneficial the treatment of HZ is: 12 hours before the vesicles are ruptured and wet in the form of open compresses with antiseptic solutions and antiseptic creams or antibiotics. If there is a wound with signs of secondary infection, antibiotic cream or ointment can be given.22

Complications of Shingles can be divided into neurological, ocular, cutaneous and visceral. The incidence of complications increases with age. The most common complication is post-herpetic neuralgia (NPH) which is defined as the presence of pain after the lesion disappears, or pain that persists for more than 1 month, 3 months, 4 months, or 6 months after the eruption disappears.23 In an epidemiological study conducted by Habel LA et al in 2013, disseminated Hz was the most common complication in patients with malignancies, 19.3% in haematological malignancies and 8.5% in solid tumour malignancies.28 Disseminated cutaneous is defined as the presence of 20 vesicles outside the primary vesicle and in adjacent dermatomes, usually preceded by internal organ involvement such as lung, liver, brain about 10% in high-risk individuals. Skin, neurological, and ocular complications account for 7.9%; 2.9%; 3.3% respectively in haematological malignancies.21 Acute and chronic skin complications are common. Apart from pigmentation and scars, bacterial secondary infections are common in the acute phase and if undiagnosed can lead to septicemia. In our case, the patient was treated with acyclovir 800 mg tablets every 4.5 hours intraorally for 10 days, gabapentin 300 mg tablets every 24 hours intraorally for 3 days and continued 300 mg every 12 hours on day 4 to day 7, neureosan® tablets every 8 hours intraorally, wound care with NaCl 0.9% compresses for 10 minutes every morning and evening and then apply mupirocin 2% ointment on the erosion area and on unruptured vesicles apply salicyc powder. Gabapentin is an anticonvulant originally developed and approved as adjunctive therapy for the treatment of partial seizures, often used for the treatment of neuropathic pain which is an analogue of gamma aminobutyric acid and binds to the 2-5 site of voltage-dependent calcium channels, thereby reducing the release of neurotransmitters.22 Human studies suggest gabapentin is beneficial for the treatment of chronic neuropathic pain and may also reduce allodynia and hyperalgesia.23 European consensus-based Hz management guidelines recommend that gabapentin can be added as an analgesic for the treatment of Hz infection if moderate or severe pain is present. Some evidence suggests that pain attenuation during the acute phase of Hz may prevent NPH, and gabapentin reduces neuropathic pain by acting on the central and peripheral nervous systems, both of which are damaged by Hz infection.24 The effectiveness of gabapentin for the treatment of NPH has been tested and there is evidence that it can improve patients’ quality of life, mood and sleep.25 Treatment using gabapentin starts at 300 mg/day and increases to 3600 mg/day if needed. A Cochrane review reported that among patients taking gabapentin at doses greater than 1200 mg/day, there was an NPH-related pain reduction effect (50% or more pain reduction) in 32% of patients, and a moderately favourable effect (30% or more pain reduction) in 46% of patients. Combination therapy of gabapentin and valacyclovir in patients with acute Hz can reduce the incidence of NPH. In terms of pharmacokinetics, gabapentin is absorbed slowly, peaking 3–4 hours after ingestion and is not metabolised by the liver and does not affect the action of liver enzymes.26,27,30

The patient showed a good response to the antiviral therapy given, the skin lesions dried up and no new lesions appeared after 4 days of treatment, but the patient still had pain. The possibility of post-herpetic pain complications is also higher in patients with malignancy.7 Skin lesions usually heal within two to four weeks, but complete healing takes more than four weeks.19

Prognosis in shingles, especially in chemotherapy recipients with lesions affecting visceral organs, mortality reaches 30%, which can worsen if the lymphocyte count decreases to < 500/mcl. Prognosis will worsen in the presence of central nervous system symptoms that appear 4 - 8 days after skin infection.4

CONCLUSIONS AND SUGGESTION
A case of Hz as high as dermatome C6-T4 sinistra in a patient with breast cancer after total mastectomy dextra has been reported. The diagnosis of Hz is based on anamnesis, physical examination and supporting examination were based on anamnesis obtained complaints appear plentiful clear liquid that is easily broken and feels like burning pain in the left chest then spreads to the back, armpit and left arm accompanied by fever. Physical examination found vital signs within normal limits, while dermatological status in the superior extremity region et axillaris et truncus anterior et posterior sinistra appeared unilateral clustered multiple vesicles with an erythema base partially broken to form crusts as high as cervical dermatome 6 to thoracic 4 (C6-T4) sinistra. The management given was antiviral given for 10 days, analgesic and systemic neurotrophic vitamins and topical therapy. Observations showed improvement on follow-up day 7, but pain was still felt. The prognosis in this patient is good because the patient is currently not undergoing radiotherapy or chemotherapy treatment for a history of breast cancer suffered by the patient.

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APPENDIX: FOLLOW UP 7th DAY TREATMENT

Gambar 1. (A-H) Regio ektremitas superior et aksilaris et trunkus anterior et posterior sinistra tampak vesikel multipel yang bergerombol unilateral yang telah pecah dasar eritem dengan krusta diatasnya setinggi dermatom servikal 6 sampai dengan torakal 4 (C6-T4) sinistra (panah kuning).