Hemorrhagic Varicella in Osteosarcoma: Case Report Is It Induced by Chemotherapy Agent or Nature of the Disease?

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Abstract: Varicella is a result of primary *varicella-zoster* virus infection and can be found worldwide. Eventhough varicella is a self-limiting disease, serious complications can occur in 2-6% cases, especially in neonatus, adults, and immunocompromised patients. The uncommon hemorrhagic complication that occurs in these patients could be the result of thrombocytopenia, increased capillary pressure secondary to cutaneous hyperemia, or bacterial secondary infection. Thrombocytopenia state can be caused by the chemoterapy agent and be worsen by the increasing antibody response to the platelets, interaction between the virus and the platelets resulting early removal of platelets by the reticuloendothelial system, or the release of the neuraminidase from the virus. Mortality rates of complicated varicella is 63%. We report 2 patients with hemorrhagic varicela in osteosarcoma in the facial region and thrombocytopenia. Both patients were clinically diagnosed with varicella and were given intravenous acyclovir 10 mg / kg bodyweight for 10 consecutive days. During treatment, there were no new vesicles, last crop of vesicles had crusted. Thrombocytopenia state was corrected with thrombocyte concentrate (TC) transfusion and fortunately no internal bleeding found.

1 INTRODUCTION

Varicella is primary infection of varicella-zoster virus (VZV). Varicella cases are distributed worldwide, but the incidence differs in climates and vaccination status (Schmader & Oxman, 2012). The incidence is expected to be 60 million cases every year (Gancheva et al., 2014). Varicella is highly contagious and could be endemic in subtropic countries and the lack of vaccination. About 90% of varicella occurred in children younger than 10 years old (Schmader & Oxman, 2012). There were approximately 11.000 hospitalization and 100 deaths caused by varicella each year before vaccination era in 2004 (Seward et al., 2002).

Varicella patients starts to be infectious from 1-2 days before exanthem appears and for 4-5 days after it appears. In immunocompromised patients, the exanthem can last longer, which means the infectious period is also prolonged. The incubation period of varicella is 10-23 days, with the average of 14 days (Schmader & Oxman, 2012; Marin et al., 2016). The major route of infection is the respiratory tract and direct contact (Schmader & Oxman, 2012; Gancheva et al., 2014; Seward et al., 2002; Marin et al., 2016).

Before exanthem appears, varicella is often preceded by 2-3 days of prodromal symptoms, though these prodromal symptoms are uncommon in young children. After the prodromal symptoms, erythematous macules appear firstly on the scalp and face, then spread rapidly to the trunk. Progressively, the macules turn into papules, vesicles, pustules, and crusts that distributed centrally on the body (Schmader & Oxman, 2012; Miller & Stephan, 1993).

Differential diagnosis includes vesicular viral exanthem, insect bites, impetigo, contact dermatitis, and disseminated herpes simplex (Schmader & Oxman, 2012; Miller & Stephan, 1993). Varicella can be diagnosed from the clinical appereance and evolution of its characteristic rash, especially if there's a direct contact with other varicella patient 2-3 weeks before (Schmader & Oxman, 2012). Tzanck smear test from the base of the vesicles shows the presence of a characteristic multinucleated giant cells but can't distinguish it from other viral infection (Leung et al., 2010; Nahass et al., 1992).

Eventhough varicella is a self-limiting disease, serious complications can occur in 2-6% cases, especially in neonatus, adults, and

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immunocompromised patients (Schmader & Oxman, 2012, Miller et al., 1993; Bonanni, 2009). The complications can occur before, during, or after the presence of rashes. Most complications of varicella can be grouped into eight major categories: (1) bacterial superinfection; (2) herpes zoster; (3) varicella-associated Reye's syndrome; (4) central nervous system; (5) pulmonary; (6) hemorrhagic; (7) therapeutic complications or exacerbation of underlying illnesses; and (8) immunocompromised patients (Miller et al., 1993). Hemorrhagic complication that occurs in varicella is frequently associated with secondary thrombocytopenia or secondary infection. The states of thrombocytopenia relate to increased capillary pressure secondary to cutaneous hyperemia causes the clinical hemorrhagic appeareance (Charkes, 1961). Mortality rates of complicated varicella is as high as 63% (Miller et al., 1993).

2 CASE

We report 2 cases of hemorrhagic varicella in osteosarcoma patients. First patient was a 16 years old girl, presented to Pediatric Emergency Unit of Cipto Mangunkusumo General Hospital (RSCM) with dark vesicles and bullous on her body from 10 days before admission. It started with 3 erythematous vesicles on the face and high fever. Within the same day, the vesicles spread to the other part of her body and turned dark. New dark vesicles still appeared 1 day before admission on the soles of the feet. She also suffered pain sensation all over her body, which made her uncomfortable and hard to sleep. The patient had not given any medication before admission, except for the paracetamol she had been taking since her first chemotherapy.

Two weeks before the first vesicles appeared, patient held her nephew who was having varicella. There was no history of applying anything before vesicles appeared. There was no history of loss of consciousness, dispnea, cough, blurred vision, or upper abdomen pain. The patient was diagnosed with nasal osteosarcoma and was on the third chemotherapy and took paracetamol regularly to reduce the pain. The patient never had varicella and varicella vaccination before.

From the physical examination, the vital signs were within normal limit. Her body weight was 60 kg and her body height was 158 cm (BMI: 24,03). We found multiple, circumscribed, discrete hemorrhagic vesicle-bullous and some black crusts all over her body. There was no lymph enlargement. Laboratories studies obtained: hemoglobin was 9,59 g/dL; leukocyte was 2,58 x 10^3/µL; platelet count was 17 x 10^3/µL; and albumin was 2,23 g/dL. Other laboratories studies were within normal limit.

The patient was diagnosed with osteosarcoma grade IV on third cycle chemotherapy and varicella with pancytopenia and hypoalbuminemia state. The patient was admitted to the isolation room and given intravenous acyclovir 600 mg every 8 hours, intravenous ampicillin-sulbactam 2 gram every 6 hours, oral paracetamol 500 mg every 8 hours, albumin 20% transfusion 2 x 100 mL, thrombocyte concentrate (TC) transfusion, and high protein diet (1,5 g/kg body weight/day).

On the fifth day of IV acyclovir, the patient was getting better, there were no new lesions, while some of the vesicles had already crusted. On the 10th day, the patient felt so much better and was excited to get home. There was no new lesions, fever, and pain. The patient was then discharged and oral acyclovir was continued until the 14th day.

Second patient was a 23 years old male. The patient was on the 5th day treatment in the ward by the Internal Medicine Department, RSCM and was consulted with hemorrhagic vesicles since 3 days ago along with fever. The patient didn't feel any pain or itch sensation. The vesicles started as red patch on the face and within 1 day, the red patch became vesicles and spread to other part of his body.

There was no history of loss of consciousness, dispnea, cough, blurred vision, or upper abdomen pain. The patient never had varicella and varicella vaccination before, nor contact with other varicella patients. The patient was already diagnosed with osteosarcoma on the mastoid region and was at the second chemotherapy with anemia, hypoalbuminemia, and thrombocytopenia states.

From the physical examination, the vital signs were within normal limit. His body weight was 70 kg and his body height was 168 cm (BMI: 24,80). We found multiple, circumscribed, discrete black vesicle-bullous on the skalp, neck, chest, stomach, back, both arms and legs. No lymph enlargement was found. Laboratories studies revealed: hemoglobin was 8 g/dL; leukocyte was 0,26 x 10^3/µL; platelet count was 25 x 10^3/µL; andn albumin was 3,21 g/dL. Other laboratories studies were within normal limit.

We diagnosed the patient as varicella in immunocompromised and thrombocytopenia state and gave him intravenous acyclovir 700 mg every 8 hours, oral paracetamol 500 mg every 8 hours, oral paracetamol 500 mg every 8 hours, intravenous meropenem 1 g every 8 hours, TC transfusion, and high protein diet (1,5 g/kg body weight/day). During

treatment, patient was getting better and there were no new lesions since intravenous acyclovir had been given. All the vesicles had already crusted on the 10th day of acyclovir.

3 DISCUSSION

Both patients were clinically diagnosed with varicella because of the characteristic rash, which began as red macules on the scalp and progressively turned into papules, vesicles, pustules, and crusts that centrally distributed. There were direct contacts with other varicella patients in the first patient, which was her nephew. The high fever and pain in the first patient were the prodromal symptoms. Tzanck smear from the base of vesicle might show multinucleated giant cells in viral infection and although it's not specific for varicella, it might be helpful in confirming the diagnosis of varicella (leung et al., 2010; Nahass et al., 1992). We did not do Tzanck smear because the diagnosis can already be made clinically. Usually the treatment is limited to acetaminophen for fever and pain, sometimes antipruritic for the itch, and maintenance of general hygiene. Varicella patients with immunocompromised are generally given intravenous acyclovir for 10-14 days, which dramatically reduces the risk of complications and formation of new lesions (Miller et al., 1993). The virus will then remain latent in sensory ganglia and could reappears as herpes zoster in 10%-15% individuals (Schmader & Oxman, 2012).

Coagulopathies are frequently associated with varicella infection through a variety of etiological mechanism. The uncommon hemorrhagic lesions in both patients could be the result of thrombocytopenia caused by the chemotherapy agent, increased capillary pressure secondary to cutaneous hyperemia, or bacterial secondary infection. Viral infection could make the thrombocytopenia worse by several mechanisms: an increased antibody response (suggesting the possibility of an autoimmune mechanism), interaction between the virus and the platelets result in early removal of platelets by the reticuloendothelial system, or the release of the neuraminidase from the virus attacks sialic acid in the platelet membrane. Patients with malignant or progressive varicella with purpura, are unable to terminate the viremia because of the changes in T-cell subsets and maybe related to inadequate production of interferon. Bleeding from the gastrointestinal tract, genitourinary tract, and mucous membranes is frequent and the mortality rate is greater than 70% (Miller et al., 1993). Fortunately both patients did not have any evidence related to gastrointestinal or genitourinary bleeding.

Varicella is highly contagious and could be endemic with attack rates 60-100%,[10,11] and for that reason, both patients were admitted to isolation room (Varicella-Zoster Infections, 2009; Heininger et al., 2006). The most common complication of varicella is bacterial superinfection (Schmader & Oxman, 2012, Miller et al., 1993; Bonanni, 2009). This superinfection could lead to septic shock in immunocompromised patients. Both patients were given broad spectrum antibiotic for severe infections (Nelson et al., 2016).

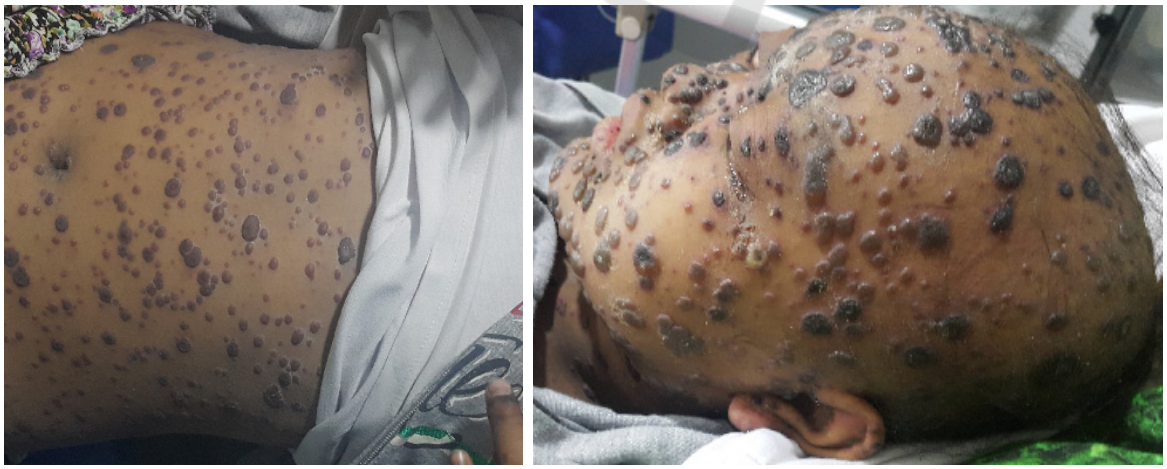

Figure 1. First patient with hemorrhagic varicella

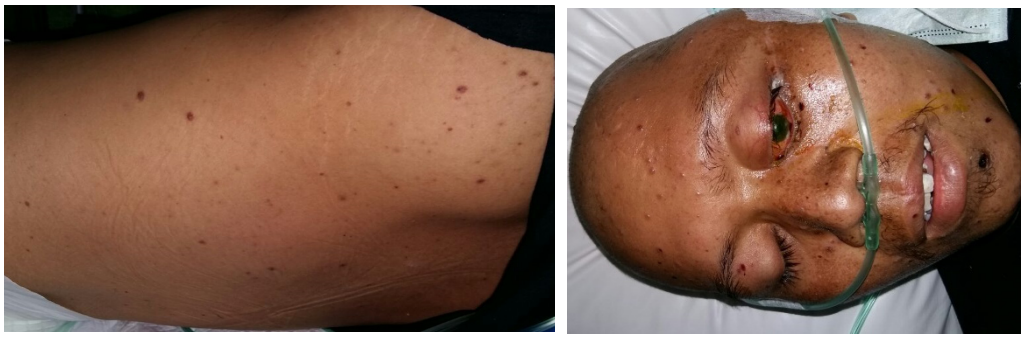

Figure 2. Second patient with hemorrhagic varicella

4 CONCLUSION

Serious complications can occur in varicella, especially those with immunocompromised state, including hemorrhagic lesions. These hemorrhagic lesions can be the result of thrombocytopenia caused by the chemotherapy agent and increased capillary pressure secondary to cutaneous hyperemia. The thrombocytopenia is worsen by several mechanism, which is the nature of the disease itself.

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