Hemorrhagic Varicella in a 41-Year-Old Woman with Evans Syndrome : Case Report

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Abstract

Background: Varicella is an infection caused by the *varicella-zoster virus* (VZV) with symptoms of an exanthematous vesicular rash and systemic symptoms. Hemorrhagic varicella commonly seen in immunocompromised patients. Evans syndrome (ES) is an autoimmune with two or more cytopenias,including autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP).

Case: 41-year-old woman complains of swelling filled with reddish fluid almost all over her body,sometimes painful and accompanied by fever. Patient also experienced vaginal bleeding resulting in anemia (Hb 8.8 g/DL) and thrombocytopenia (platelets 34,000/uL). Dermatological status of the generalized,multiple hemorrhagic vesicles with an erythematous base,partially ruptured. Tzank test revealed multinucleated giant cells. Patient suffered AIHA and received therapy with methylprednisolone 4 mg/day and mycophenolic acid 2x500 mg/day.

Conclusion: We report a case of hemorrhagic varicella in a 41-year-old woman with Evan's syndrome with concurrent features of AIHA and ITP. Dermatological status of the generalized, multiple hemorrhagic vesicles with an erythematous base,some of ruptured with erosions. Tzank test revealed multinucleated giant cells. Patient was treated with acyclovir 5x800 mg for 7 days,2% salicylic acid and 0.5% menthol applied every 12 hours and mupirocin 2% ointment applied twice a day on the erosion area and clinical improvement was found after 17 days of therapy.

Key words: *Acyclovir, Evans Syndrome, Tzank test, Haemorrhagic Varicella*

Introduction

Varicella is an infection caused by *Varicella-zoster virus* (VZV) with symptoms of an exanthematous vesicular rash and highly contagious. Varicella is more common in children, but can also occur in adults or in certain conditions like immunocompromised.[1] Immunocompromised patients may develop severe complications such as hemorrhagic varicella, encephalitis, pneumonitis and thrombocytopenia.[2] Evans syndrome is an autoimmune condition that presents with AIHA and/or ITP with or without immune neutropenia. Evans syndrome was first reported in 1951 and often accompanies varicella.[3]

Sharma et al. reported the incidence of hemorrhagic varicella worldwide was estimated at 3.3% of the total varicella cases with an increase in mortality of 7-10%.[4]

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Wu et al. reported that there are 2,794 varicella cases in the period 2008 -2017.[5] Sondakh et al. reported that there were 77 varicella cases occurred in 2010-2015 at Cipto Mangunkusumo Hospital Jakarta.[6] Incidence of Evans Syndrome is quite rare found. Mannering et al. reported that the incidence of Evans Syndrome in the world ranged from 0.5-1.2/1,000,000 people per year.[7] Tanaka et al. reported the occurrence of 8 cases of Evans Syndrome associated with varicella infection.[8]

Clinical manifestations of hemorrhagic varicella can appear all over the body. The clinical manifestations of Evans syndrome are associated with anemia and thrombocytopenia which include pallor, weakness, fatigue, jaundice, petechiae, ecchymosis, bleeding gums, epistaxis and other bleeding.[9] The diagnosis of VZV is made based on the clinical picture, Tzanck test, polymerase chain reaction (PCR), or enzyme-linked immunosorbent assay (ELISA).[9] The diagnosis of Evans syndrome can be established by a Coomb's test which is positive for hemolytic anemia.[9] Differential diagnoses of varicella include herpes zoster and disseminated herpes zoster.[10]

Hemorrhagic varicella therapy is acyclovir 5x800 mg/24 hours which is useful for reducing the rash, constitutional symptoms and inhibiting viral replication.[11] There are no specific guidelines for the management of Evans Syndrome, it's just symptomatic therapy with corticosteroids and intravenous immunoglobulin in severe cases.[9]

The purpose of this case report is to know that varicella can show atypical clinical manifestations in the form of hemorrhagic varicella, association with AIHA and Evans syndrome.

Case

Patient Mrs. H, 41 years old, came with swelling filled with reddish fluid in several parts of the body. Complaints appeared since 4 days ago in the form of blisters around the groin and itching, which then spread to body and face. She also felt weak one day later accompanied by fever and difficulty sleeping. Patient has a history of AIHA since 4 years ago.

The patient then went to a general practitioner and was advised to do laboratory tests. The results showed a hemoglobin value of 4.6 g/dl (14.0-17.5 g/dl), then the doctor recommended blood transfusion, but after blood transfusion the hemoglobin level became lower, 2.9 g/dl. The patient was consulted to an internal medicine specialist and diagnosed with AIHA, received oral methylprednisolone therapy 4 mg/day and cellcept® (mycophenolate mofetil) 500 mg orally twice daily routinely. The patient was declared cured in April 2018 and oral medication was discontinued, but in December 2018 there was vaginal bleeding of approximately 500 ml. Patient experienced a clinical deterioration, so she was hospitalized again at the PKU Muhammadiyah Surakarta Hospital for five days and from the laboratory result, it was found that platelets were 30,000 gr/dl (150,000 - 450,000 gr/dl). Patient underwent a Coomb's test and the results were positive, then she was routinely monitored and received Cellcept® (mycophenolate mofetil) 500 mg orally 2 times a day. Patient had no history of allergies, atopy, hypertension or diabetes mellitus.

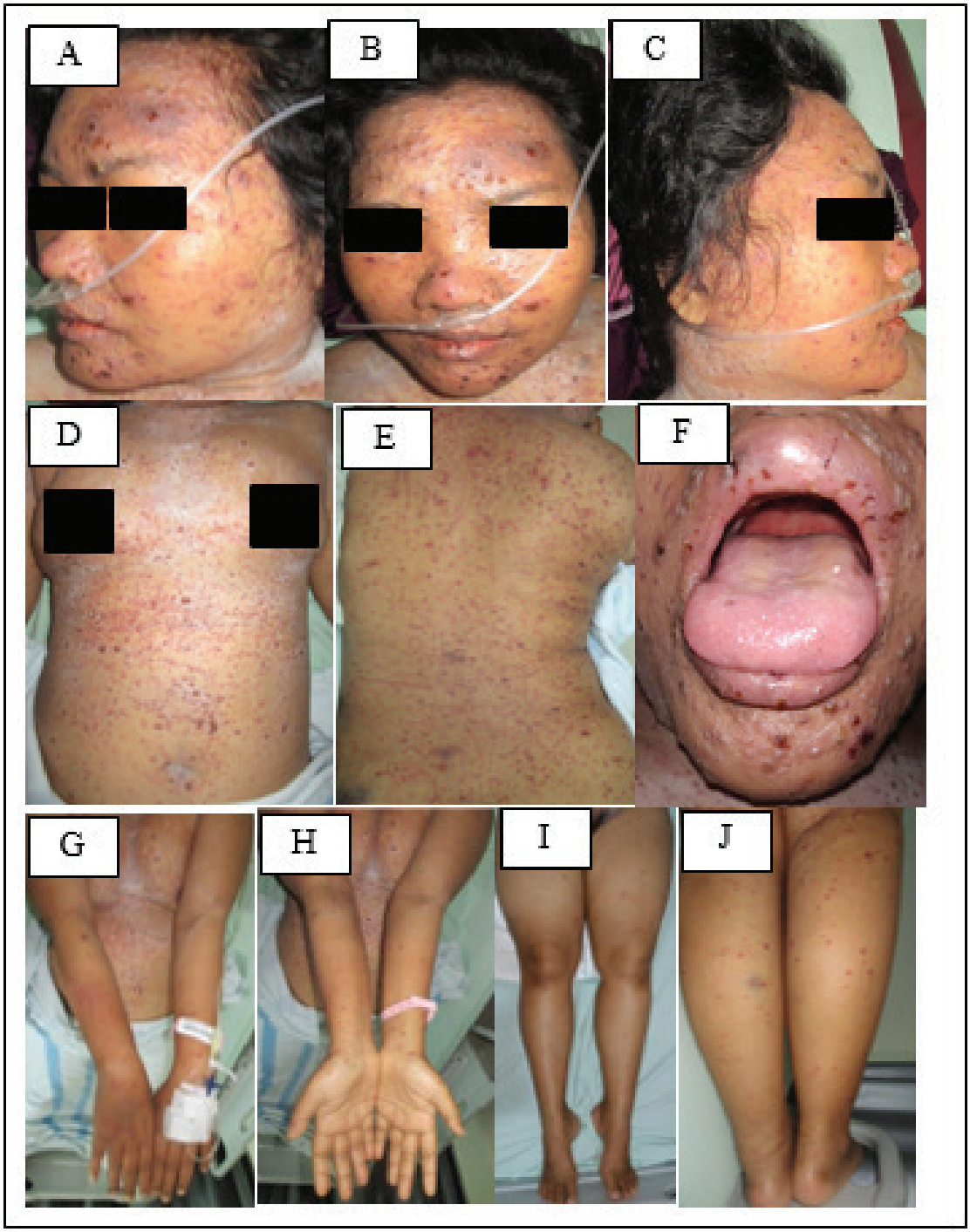

Figure 1. A-J. The generalized region showed multiple polymorphic hemorrhagic vesicles with an erythematous base and varied in size with a diameter of 0.2-0.5 cm which were partially eroded and covered with blackish crusts.

Physical examination showed that the patient was seriously ill with normal vital signs and a pain scale of 8. Dermatological status in the generalized region showed multiple polymorphic hemorrhagic vesicles with erythematous base with varying diameter of 0.2-0.5 cm and some had erosions covered with black crusts (Figure1). Patient was diagnosed with hemorrhagic varicella and differentially diagnosed with disseminated

herpes zoster based on the history and physical examination.

The Tzanck test showed multinucleated giant cells (Figure 2). Laboratory result showed anemia with a hemoglobin level of 8.8g/dL (14.0-17.5g/dL), leukocytosis with a result of 15,800/µL (4,500-14,500/µL) and thrombocytopenia with a result of 34,000/µL (150,000-450,000/µL), while other examination results were within normal limits. Based on the results of blood chemistry examination, there was an increase in SGOT and SGPT values, the SGOT value reached 361u/l (<35u/L), while the SGPT value reached 804u/l (<45u/L). The urinalysis showed macroscopic examination results pH 5.0 (5.0-7.5), leukocytes 500/uL (negative), protein +2 (negative), urobilinogen +2 (normal), bilirubin +1 (negative) and erythrocytes +2 (negative). , while microscopic examination showed leukocytes 63.6/lpb (0-12/lpb), crystals 5.2/uL (0.0/uL), yeast like cells 226.6/uL (0.0/uL) and erythrocytes 40-42/lpb (0- 8.7/lpb). There was an increase in LDH levels of 2243 u/l (210-425 u/l), reticulocyte levels of 2.06% (0.5-1.5%), total bilirubin levels of 1.41 mg/dl (0.2-1.2 mg/dl) with a direct bilirubin value of 0.77 mg/dl. dl (0-0.4 mg/dl) and indirect bilirubin 0.64 mg/dl (0.3-1.1 mg/dl) and PT and APTT were within normal limits.

The patient was hospitalized and treated together with internal medicine and anesthesia for the management of Evans Syndrome and pain complaints. Based on the history, physical examination and supporting examination, our patient was diagnosed with hemorrhagic varicella. The patient was treated with oral acyclovir 800 mg every 4 hours for 7 days, 2% salicylic acid cream + 0.5% menthol topical every 12 hours applied to the lesion of the vesicle, mupirocin ointment applied to the area of erosion every 12 hours and paracetamol 500 mg given if the patient had a fever. The patient was managed by the internal medicine department with injection of methylprednisolone 250 mg 24 hours, levofloxacin injection 750 mg 24 hours, cetirizine oral tablet 10 mg every 24 hours, folic acid tablet 1 mg oral 24 hours and calvit D (Ca hydrogen phosphate 500 mg, cholecalciferol 133 IU) tablet orall y every 12 hours. Anesthesia department provided additional therapy in the form of injection of morphine 680 mcg per 24 hours for pain relief.

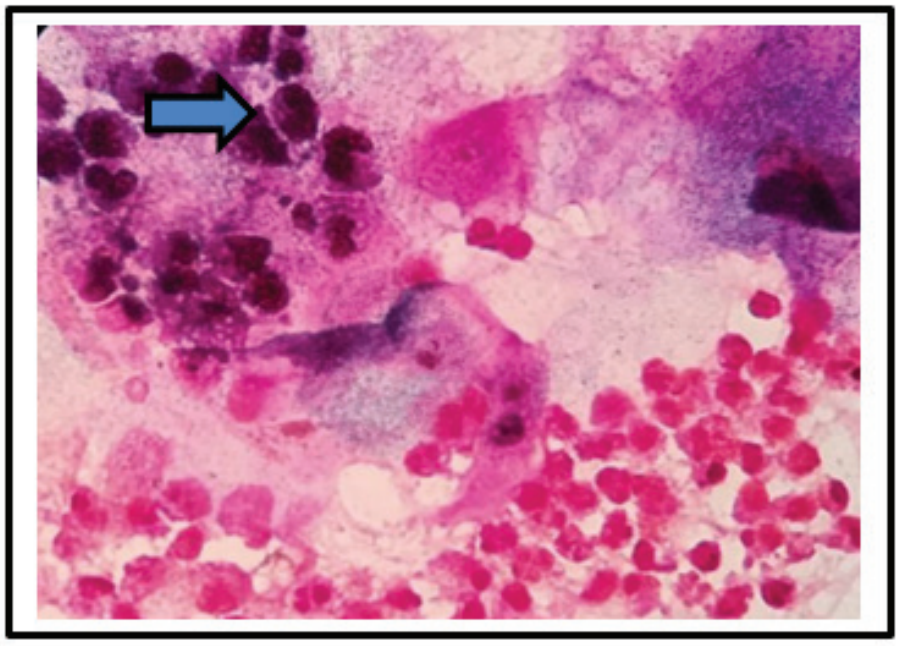

Figure 2. In Tzanck's smear, multinucleated giant cells were found (blue arrow).

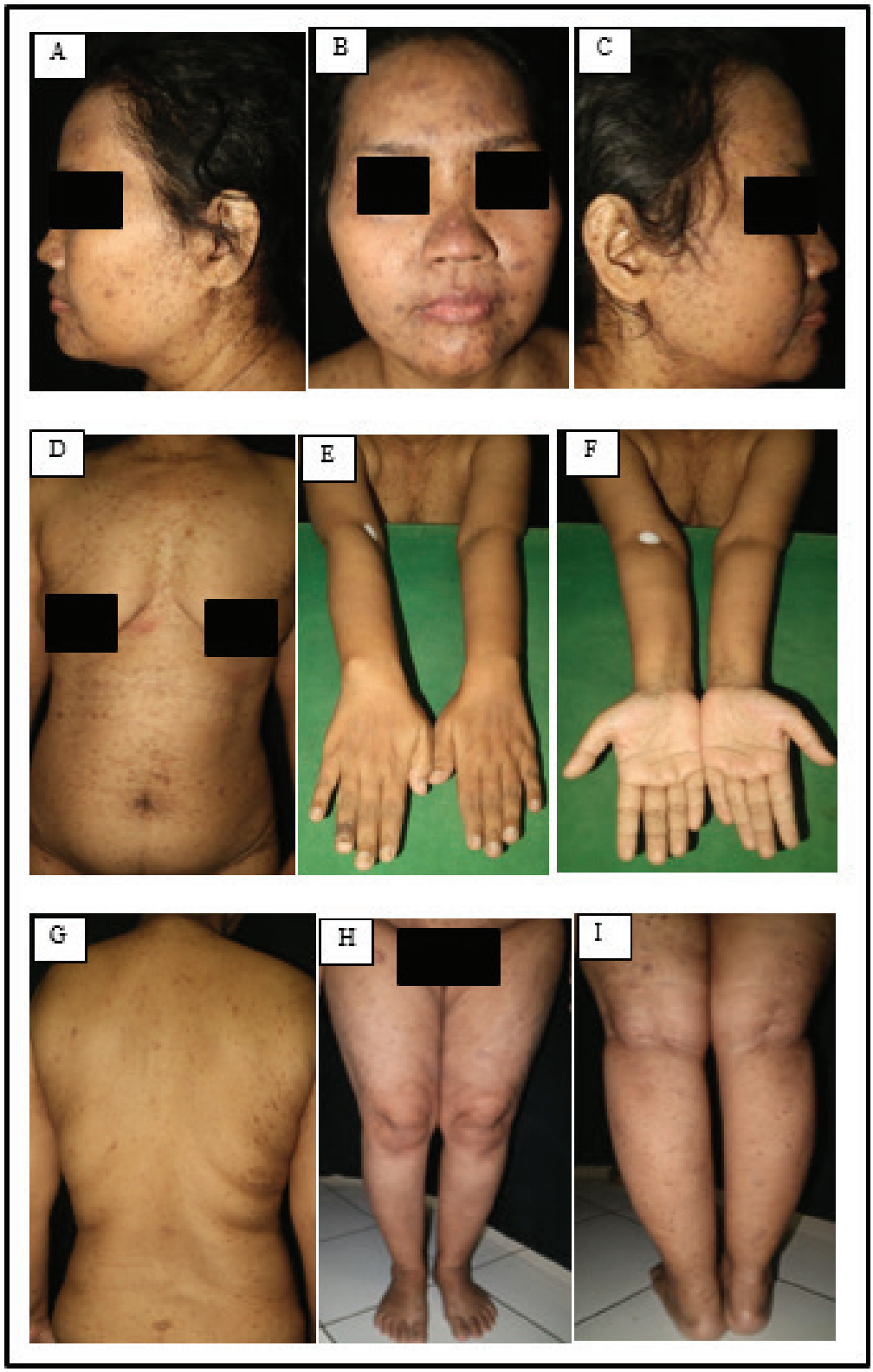

Figure 3. A-I. Day 17 after therapy. The generalized region shows macules and multiple discrete hyperpigmented patches.

Discussion

Varicella is caused by primary infection of VZV. Varicella is a self-limiting disease, but it can be life-threatening. Varicella is a highly contagious disease. Varicella spreads through respiratory tract and direct contact with lesions. The incubation period for varicella ranges from 10-21 days with an average incubation period of 14 days.[4,9] Evans syndrome is a rare condition that is a continuation of ITP and AIHA with the result positive Coomb's test of unknown etiology. Evans syndrome mostly occurs at a young age, more often in women than men, age range of 23-50 years.[9]

Varicella in immunocompromised patients may have atypical manifestations in the form of hemorrhagic varicella.[4] Patients with Evans syndrome have main symptom, namely thrombocytopenia. The pathological process of thrombocytopenia is the formation of autoantibodies that react with platelet surface antigens. If these autoantibodies bind to platelets, they will cause platelets to exit the circulation through phagocytosis by the reticuloendothelial system. This results in shortened platelet lifespan resulting in thrombocytopenia.[9] Hemorrhagic varicella is associated with thrombocytopenia where vesicular eruptions in varicella turn into hemorrhagic vesicles if the patient suffers from thrombocytopenia.[4]

Clinical manifestations of varicella begin with prodromal symptoms followed by the appearance of skin lesions. Varicella skin lesions begin with the appearance of macules that develop into papules, vesicles, pustules, and crusts.[12,14] Vesicles in varicella are round-shaped oval, filled with clear fluid, and overlying erythematous skin. The vesicle fluid can turn into pustules, then rupture and dry into crusts. The skin rash is dominant on the trunk and head region which then spreads to the extremities centrifugally. At first, blisters appeared around the groin that felt itchy, then appeared vesicles in the groin area, body and face accompanied by fever. Dermatological status of patient in the generalized region showed multiple polymorphic hemorrhagic vesicles with an erythematous base and varying diameter of 0.2-0.5 cm, some were eroded and covered with black crusts. This clinical picture is consistent with that described in the literature.

The diagnosis of varicella is made based on the clinical manifestation which is reinforced by a history of contact with varicella sufferers within a period of 2-3 weeks.[9] Tzanck test that shows multinucleated giant cells will confirm the diagnosis.[12] In this case, the Tzanck test results from a new vesicle lesion on the patient's right arm revealed multinucleated giant cells. The Tzank test of the patient is consistent with the literature.

The diagnosis of Evans Syndrome is made based on clinical manifestations and anamnesis which include a history of disease progression, family history of autoimmune disorders and exclude risk factors that may predispose infection, malignancy, autoimmune disease, vaccination history and drug use. The physical examination focused on signs of anemia or thrombocytopenia. Supportive laboratory examinations such as complete blood count, peripheral blood test will show anemia, thrombocytopenia, reticulocytosis, poikilocytosis, especially due to the presence of spherocytes. Elevated indirect bilirubin and lactate dehydrogenase may also be found. Positive results from the Coombs test indicate ongoing immune hemolysis.[3,9] In this case, the clinical picture of vaginal bleeding found indicated the presence of thrombocytopenia which was in line with the laboratory results obtained, namely a platelet count of 34,000/µL (150,000-450,000). /L). The clinical manifestation of pallor and weakness which is a symptom of anemia is also found and hemoglobin level was 8.8g/dL. This patient exhibited concurrent clinical features of AIHA and ITP suggestive of mixed-type Evans syndrome. The lab result showed an increase in LDH, namely 2243u/l (210-425u/l), Reticulocyte levels 2.06% (0.5-1.5%), PT and APTT were within normal limits. The definitive diagnosis of Evans Syndrome is related to a positive Coomb's test for hemolytic anemia.[13] In this case, a positive Coomb's test result, physical examination, and laboratory finding was used as the basis for diagnosing mixed type Evans Syndrome.

The differential diagnosis in this case was disseminated herpes zoster (HZD). The clinical picture of HZD is the initial lesion in the form of herpes zoster localized in one or several dermatomes in 90% of cases which then in 1-12 days will spread generally. This is the main difference between disseminated herpes zoster and varicella that occurs in adulthood. In this case, the initial lesion of herpes zoster was not localized in dermatome, although the Tzanck test revealed multinucleated giant cells, so the diagnosis of disseminated herpes zoster could be ruled out.[1,10]

The first-line therapy for VZV is acyclovir. The dose for adult patients is 20 mg/kg with a maximum dose of 800 mg 5 times a day. Antiviral aims to stop the formation of new lesions and shorten the duration of rash, fever and constitutional symptoms. Immunocompromised patients are recommended to be given acyclovir injection therapy at a dose of 10-15 mg/kg given every 8 hours intravenously for 7 days.[12] In some cases that do not respond well to acyclovir, other therapeutic options can be given, namely brivudine, foscarnet, or vidarabin.[15] Topical therapy is symptomatic therapy and can be given depending on the stage of the disease. Powdering can be applied to vesicle lesions and to erosion, topical antibiotics can be given to prevent secondary infection. Antipyretics are sometimes needed if there are complaints of fever.[12]

An exact algorithm for Evans Syndrome treatment has not been postulated to date. Some literature mentions that the first-line therapy is corticosteroids. In acute life-threatening conditions, packed red cell (PRC) transfusions can be given. Intravenous immunoglobulin (IVIG) may be given in cases with thrombocytopenia as the main laboratory finding in these cases. We treated this patient with an internist and anesthesiologist. Our management is oral acyclovir 800 mg every 4 hours for 14 days and administration of 2% salicylic acid cream + 0.5% menthol every 12 hours for vesicular lesions and mupirocin ointment for erosion areas every 12 hours and additional 500 mg paracetamol is given if needed. Management given by internal medicine colleagues is injection of methylprednisolone 250 mg per 24 hours, injection of levofloxacin 750 mg per 24 hours, cetirizine oral tablet 10 mg per 24 hours, folic acid tablet oral 1 mg per 24 hours, calvit D (ca hydrogen phosphate) 500 mg, cholecalciferol 133 IU) tablet orally every 12 hours, while an anesthesiologist friend gave morphine injection therapy 680 mcg per 24 hours to treat pain in patients.

The patient was allowed to go home by the internal medicine department after the tenth day of treatment in an improved condition. The patient was re-controlled to the skin clinic after one week after hospitalization with the condition of the lesions having improved with the remaining lesions in the form of hyperpigmented macules and plaques and erosion covered by blackish crusts in some areas. (Figure 3)

Conclusion

In this paper, we report a case of hemorrhagic varicella in a 41-year-old woman with Evans syndrome. The diagnosis is based on history, physical examination and investigations. Autoanamnesis, there were complaints of watery splinting which began with the appearance of abrasions in the groin area since 4 days before admission to the hospital. Physical examination revealed that the dermatological status in the generalized region showed multiple polymorphic efflorescence of hemorrhagic vesicles with an erythematous base and varied sizes (0.2-0.5 cm in diameter), some of which had erosions covered with black crusts. The results of the Tzanck test revealed multinucleated giant cells. The patient was treated with oral acyclovir 800 mg every 4 hours, 2% salicylic acid + menthol 0.5% topical every 12 hours for vesicular lesions, mupirocin ointment for eroded areas every 12 hours and additional 500 mg paracetamol was given if the patient developed a fever. The prognosis for this patient is dubia. The control patient one week later with the condition of the lesion has improved.

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