Challenges in administering immunosupressive therapy in severe bacterial infection interfering crisis and refractory childhood systemic lupus erythematosus

Dewa Ayu Angga Rainingsih*, Ketut Dewi Kumara Wati, I Wayan Gustawan, Gusti Ayu Putu Nilawati

ABSTRACT

Background: Childhood systemic lupus erythematosus (cSLE) mostly come with severe manifestation compared to the adult. Infection aggravated the multisystem inflammation and interfering immunosuppressive agent protocol.

Case: A 12-year-old girl was hospitalized for a month with massive edema and fever after being diagnosed with nephrotic syndrome and taken prednison for four weeks. The patient was completely bedridden, presented with hypertension, large erythematous striae across the trunk and limbs, and darkened skin. Further evaluation showed the EULAR/ACR classification criteria for SLE with score of 26. Cellulitis was suspected when a red, pinprick-sized papule appeared on the patient’s right leg be increased significantly in size within two hours. Following the collection of a wound culture and blood culture specimen, triple antibiotics were given. Seven days after the wound has healed, administered of cyclophosphamide was started. Cyclophosphamide is used as an emergency treatment for lupus crises, as she experienced seizure and delirium. Seven days after cyclophosphamide administration, the wound was revived. Initial blood and wound cultures indicated an infection caused by Serratia marcescens; however, the second wound culture revealed infections caused by Klebsiella oxytoca and Enterobacter cloacae. We commenced Meropenem based on a sensitivity test to establish protection for the following administration of high-dose methylprednisolone with rituximab and cyclophosphamide. The lupus crisis was precipitated by an infection-induced inflammatory response. On day 17, after the calf and back wounds were completely healed, the antibiotic was withdrawn. In order to protect organ functionality, physiotherapy and nutritional support were employed.

Conclusion: Clinicians need to be mindful and closely observe patient with severe SLE accompanied with infection to balancing intervention for immunosuppressant therapy and antibiotic.

Keywords: systemic lupus erythematosus, infection, immunosuppressive therapy.


INTRODUCTION

Systemic lupus erythematosus (SLE) is a severe, chronic autoimmune disease that causes inflammation and eventual damage to a wide array of organ systems, including the kidney, joint, skin, heart, lung, hematological, nervous system, and blood vessels. There is a likelihood that lupus is a complex illness with an unknown origin and major immune abnormalities. Its genesis has been attributed to hormonal, genetic, and environmental factors. SLE is a very uncommon condition in childhood, but its frequency increases during adolescence; roughly 20% of persons with SLE have symptoms before the age of 16 years. SLE often manifests between the ages of 5 and 15, and is uncommon in children younger than 5 years old. Prior to puberty, the female-to-male ratio is 4.5-5:1, however it increases to 9-10:1 following puberty.1-3

It is difficult to identify lupus erythematosus due to the lack of a diagnostic test that is unique to the condition as well as the wide variety of clinical symptoms and signs. Clinicians have traditionally relied on the criteria established by the American College of Rheumatology (ACR) for classifying SLE patients. These criteria were preliminary developed in 1971, revised in 1982 and updated in 1997. In order to get around the restrictions imposed by the ACR criteria, a child is considered to have SLE if at least four of the eleven criteria are met. SLICC criteria were established in 2012 and the last in 2015 by the systemic lupus international collaborating clinics (SLICC). These criteria are more sensitive than ACR criteria, although they are less accurate. Eleven clinical features and six immunologic components make up the SLICC criteria. The Executive Committee...
of the European League Against Rheumatism (EULAR) and the Board of Directors of the American College of Rheumatology (ACR) have both suggested updated criteria for verified SLE in 2019. When ANA titer ≥ 1:80 and fulfilled clinical and immunology criteria, we can applied this criteria. SLE classification requires at least one clinical criterion and fulfilled ≥ 10 points.2,4

The appropriate management of SLE requires a multidisciplinary approach. Therapies suited to organ involvement may necessitate collaboration between rheumatologists, general pediatrics, and other experts such as nephrologists and psychiatrists. Immunosuppressive drugs is still be the main therapy for SLE.5 Managing disease activity, avoiding flare-ups, preventing damage, and minimizing iatrogenic side effects while boosting patient quality of life are the treatment aims. The kind and degree of organ involvement in systemic lupus erythematosus (SLE) are used to determine how much of an immunosuppressant medicine should be taken orally or given intravenously. Immunosuppressive treatment is linked to a wide variety of iatrogenic side effects, some of which include an altered glucose metabolism, adrenal insufficiency that requires a stress dose, cataracts, glaucoma, avascular necrosis of the bones, osteoporosis, poor growth, and early atherosclerosis. In addition to this, immunosuppressive treatment is a significant risk factor for the development of infections. As a result, treating systemic lupus erythematosus (SLE) requires a persistent effort to lower the dosage of immunosuppressant medication to the barest minimum required to keep SLE under control. Infectious organisms, such as viruses, bacteria, parasites, and fungi, also play a significant part in the process of autoimmunity developing. Several disorders are known to contribute to abnormal immune responses in genetically susceptible individuals through molecular mimicry, epitope spread, or other means.6 Clinicians need to be mindful and closely observe patients with severe SLE and avoid infection as much as possible due to the great barrier in administering immunosuppressant therapy.

**CASE**

A female, 12 years old, Balinese, came to the emergency ward at Prof. DR. I.G.N.G Ngoerah Hospital in Denpasar on 2nd August 2020 with chief complaints of swelling since a month before admitted to hospital. She was treated at T hospital with diagnosis nephrotic syndrome and was prescribed prednisone for 4 weeks. At the time of her initial admission to the Prof. DR. I.G.N.G. Ngoerah hospital, she was diagnosed with nephrotic syndrome and treated by a nephrologist. The patient was bedridden and came with hypertension, large erythematous striae with seeping across the trunk and limbs, and darkened skin. On the second hospital day, a patient developed a fever. On the third day of hospitalization, she consulted to the Allergy and Immunology consultant with plans to conduct laboratory tests to confirm the diagnosis of autoimmunity. The patient started having red pin point papule over right calf which massively enlarged within two hours. The wound was red in color with some pus and blood. Fever was stagnant and the condition of the patient were worsened. We took for wound culture, blood culture, and giving triple antibiotic. The fever and the wound was improve and the antibiotic stop at 7th day of administration. When the patient was free from fever for 2 days, we started giving cyclophosphamide as immunosuppressant agent with standard dose, but she was experience seizure followed with delirium, and we giving the remaining dose for crisis SLE. The condition was improving only for 7 days. The temperature was high again reaching 39°C, followed with progressively recurrent cellulitis at right calf. The rash appeared at face. Both legs was swollen. The striae over abdomen filled with fluid and look like bullous striae. The bullous striae enlarge to the back area and she shout loudly due to pain. She was not fully alert. At that time we giving meropenem according to sensitivity test from the second wound culture, and decided to administering immunosuppressant, that was high dose methylprednisolone followed by cyclophosphamide and rituximab due to crisis SLE.

The patient’s physical examination revealed that she is very unwell with delirium. The vital signs indicated hypertension, tachycardia, tachypnea, and a high body temperature. The nutritional state was obese. The conjuctiva are pale, there are no swollen lymph nodes, and the heart’s sound is muffled, as determined by a thoracic examination. The first and second heart sounds are normal and free from murmur. Lungs are within normal parameters. On abdominal inspection, bullous striae were seen over the belly. Backwards, there were also bloody bullous striae. No inguinal lymph node enlargement. The right calf felt heated and there was a pus-filled wound on the right calf. Upper and lower limb were swollen.

Trend of leucocyte, lymphocyte, hemoglobin, and platelets was showed in figure 1 and 2, the hemoglobin level was normal on the first time she was admitted, but decrease on the fourth day of admission. The urinalysis showed proteinuria (+4) with leukocyturia and erythrocyturia. The albumin was low (1,5 g/dL) with high total cholesterol (630 mg/dL) and normal renal function, so in the early patient was diagnosed with nephrotic syndrome. The SLICC collaboration score at that time was 1 from proteinuria, but when the hemoglobin decrease followed by thrombocytopenia, the bloodsmeared showed anisocytosis that proved hemolytic process, and the chest X ray showed congestive pulmonum with bilateral pleural effusion, the SLICC score become 5. The procalcitonin was high (41,72 ng/mL) when the cellulitis enlarged massively. The blood culture and wound culture showed the same bacteria, Serratia marcescens. Administering of triple antibiotic (cefoxazone sulbactum, amikacin, and metronidazole) giving improvement on clinical feature and laboratory. Procalcitonin become 2,51 ng/mL. The result of ANA IF was nuclear homogenous 1:1000, anti DsDNA was increase, 202.3 IU/ml and the complement 3 was low, 56,5 mg/dL. The total SLICC score with this results was 9, the total score for EULAR/ACR criteria was 26, and we started giving immunosuppressant therapy on 10th day of treatment when the infection was improve. Cyclophosphamide standard dose as much as 500 mg was administered, and after few hours she experienced seizure that indicating cerebral lupus. The remaining cyclophosphamide dose
for crisis SLE (total 500 mg/BSA) was administered. On the seventh days after administering cyclophosphamide, there was decreasing of consciousness, fever, enlarged of old cellulitis with bloody bullous striae over abdomen and trunk. The profile of CBC was worsened with leucopenia, lymphopenia, anemia, and thrombocytopenia. The wound culture showed *Klebsiella oxytoca* and *Enterobacter cloacae* infection and we started giving Meropenem according to sensitivity test followed with highdose methylprednisolone with rituximab plus cyclophosphamide institution.

**DISCUSSION**

Systemic lupus erythematosus, often known as SLE, is a chronic autoimmune illness that can affect any organ system. This condition is also associated with a considerable risk of morbidity and death. Childhood-onset systemic lupus erythematosus (cSLE) is a rare disease with a prevalence of 3.3–8.8 per 100,000 children and an incidence of 0.3–0.9 per 100,000 children-years.1 A higher incidence of cSLE has been reported in Asians, African Americans, Hispanics, and native Americans.2,3 When compared to two other more prevalent childhood autoimmune diseases, Juvenile Idiopathic Arthritis and type 1 Diabetes, SLE can be difficult to diagnose, particularly if the usual malar rash is absent. However, an astute clinician who evaluates SLE in the presence of an unusual constellation of symptoms is able to recognize crucial patterns of disease presentations that are required for making the diagnosis. Expert rheumatologists can make a clinical/laboratory diagnosis of SLE, however there are no diagnostic criteria for early identification at the moment. The 1997 American College of Rheumatology (ACR) criteria, its additional criteria, and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria are meant to define SLE but are not diagnostic. When the ACR criteria are unable to diagnose SLE, the complex/extended 2012 SLICC criteria may be used. The most recent diagnostic criteria for SLE are the “2015 SLICC revised criteria for SLE” Four or more points indicate a conclusive diagnosis of SLE; three points indicate a very suggestive diagnosis, two points indicate a probable diagnosis, and one point suggests a possible diagnosis.7 European League Against Rheumatism (EULAR) Executive Committee and the American College of Rheumatology (ACR) Board of Directors have proposed new criteria for established SLE in 2019. When ANA an titer ≥ 1:80 and fulfilled clinical and immunology criteria, we can applied this criteria. SLE classification requires at least one clinical criterion and fulfilled ≥ 10 points.4 In this case, patient female 12 years old with diagnosis of nephrotic syndrome on the first time she admitted. During hospitalization she fulfilled criteria for cSLE with score of SLICC criteria of 9 and EULAR/ACR criteria score was 26.

Patients diagnosed with cSLE have
a 50–75% chance of developing renal involvement, and more than 90% of those who do acquire renal illness do so within 2 years of receiving their diagnosis. Initial manifestations of renal disease can range from mild proteinuria and microscopic hematuria to proteinuria in the nephrotic range, urinary casts, severe hypertension, peripheral edema, renal insufficiency, and acute renal failure. Mild proteinuria and microscopic hematuria are the most common initial manifestations of renal disease. Although the renal interstitium is affected infrequently, systemic lupus erythematosus (SLE) most commonly affects the glomerulus (also known as “lupus nephritis”). Additionally, SLE can affect both the central nervous system and the peripheral nervous system, resulting in 19 different neuropsychiatric lupus (NPSLE) syndromes. Within two years of being diagnosed with cSLE, around 85 percent of individuals will acquire NPSLE. It is estimated that up to 65% of people with cSLE will develop NPSLE at some point over the course of their disease.9,10 In this case, we found the condition supporting for diagnosis of lupus nephritis (proteinuria, cast erythrocyte and hypertension) and neuropsychiatric lupus as seizure experienced.

Patients who have systemic lupus erythematosus are immunocompromised as a result of immune dysfunction that is inherent to the disease as well as the frequent use of high-dose corticosteroids and other immunosuppressive treatment.12 Secondary infection is a significant and common cause of morbidity, and infection should be considered in the differential diagnosis of any patient who has a suspected SLE flare. A high CRP level is indicative of the presence of bacterial infections, which make up the majority of infections (between 60 and 80 percent of the time). Because patients with SLE have a limited resistance to encapsulated bacteria such as pneumococci, meningococci, hemophilus influenza type B, and salmonella, the majority of bacterial infections need to be treated with antibiotics that are administered intravenously. However, individuals with SLE do not have the required specific antiplyosaccharide IgG2 response to the capsule, which provides protection against direct complement-associated lysis. It is common knowledge that viral infections can have symptoms that are quite similar to disease flares, such as normal or slightly raised CRP levels. Systemic cytomegalovirus (CMV) infections are recognized, and it is known that immunocompromised cSLE patients are more likely to suffer from severe or fatal symptoms as a result of these infections. They may manifest as a fresh infection or more frequently, as a reactivation of a preexisting illness.11,12

Study by Torrente-Segarra et al. found serious infection was associated with female sex (RR 2.4, 95% CI 2.2–4.7), renal involvement (RR 2.8, 95% CI 2–4.1), SLEDAI index >4 (RR 3, 95% CI 2–4.5), and use of immunosuppressant (OR 2.55, 95% CI 1.44–4.5).12 In this case, the patient has several predisposing factors for infection such as female sex, renal involvement, SLEDAI index >4, and use of immunosuppressant. She experienced severe infection manifested as cellulitis and bacteremia.

Fever is a common symptom among children who have SLE, and it can be difficult to tell the difference between an SLE flare and a febrile illness. Infections are one of the leading causes of death among children with SLE in Taiwan.11 Additionally, fever is a common symptom among children who have SLE. It is possible for some infections to cause systemic symptoms that are similar to those of SLE. These symptoms may be superimposed on an existing SLE condition or may cause an SLE condition to worsen. In one study, a delay in antimicrobial therapy of more than 24 hours increased hospitalized SLE patient mortality by a factor of 12; therefore, early identification and treatment of infections is essential.11 The interaction between infection and SLE is complex, as viral, bacterial, parasitic, and fungal pathogens can trigger SLE disease activity via molecular mimicry. Consequently, early identification and treatment of infections is essential. The relevance of infectious agents in the start, progression, and exacerbation of SLE has been shown via extensive study on the causal link between infection and autoimmune disease. In order to distinguish between current sickness and infection, physicians must often rely on their treatment decisions on clinical judgment and test indicators. Until now, the majority of such study has been done on adult populations, but there are no data on pediatric SLE.11

Antibodies that target double-stranded DNA (also known as anti-dsDNA Ab), the complement system, antibodies that target extracellular nuclear antigen (also known as anti-ENA Ab), cytokines, and chemokines have all been implicated as potential biological indicators of SLE flares in a number of different research projects. In addition, it has been observed that classic biomarkers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin (PCT), in addition to newly discovered biomarkers, are able to predict infection in SLE patients. Recent research has concentrated on the use of biomarkers to differentiate between a disease flare and an infection in febrile SLE patients. However, the majority of medical professionals are in agreement that no single biomarker has sufficient predictive value for both occurrences, and this is a limitation of the field. When compared to healthy controls,
the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are significantly higher in individuals diagnosed with systemic lupus erythematosus (SLE). In addition, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score is positively correlated with both of these ratios, which is a plus. In spite of this, there is a school of thought that suggests the NLR might be a helpful marker for improving the diagnostic accuracy of infection in SLE patients. On a worldwide scale, the use of a single biomarker to discriminate between infectious illness and other types of activity is extremely unlikely to be sufficient. New scores that incorporate combinations of several biomarkers may yield superior differentiation solutions. On the one hand, SLE Damage Index (SDI), fever temperature, CRP, procalcitonin (PCT), lymphocyte percentage, neutrophil to lymphocyte ratio (NLR), hemoglobin, platelet, and RDW to platelet ratio (RPR) are predictive of flare (combined calculated AUC of 0.8964 and sensitivity of 82.2% and specificity of 90.9%), and on the other hand, SDI, fever temperature, CRP, procalcitonin (PCT), lymphocyte percentage, NLR, hemoglobin, and renal score in SLEDAI are predictive of infection (combined calculated AUC of 0.7886 and with sensitivity of 63.5% and specificity of 89.2%),. In this case, the patient has activity predict score was 1,261 (more than 0.77665 as cut off for flare) and infection predict score was 2,258 (more than 0.58286 as cut off for acute infection), so patient was in flare and acute infection.

The appropriate management of cSLE requires a multidisciplinary approach. Therapies suited to organ involvement may necessitate collaboration between rheumatologists, general pediatrics, and other experts such as nephrologists and psychiatrists. Controlling cSLE activity, preventing flares, avoiding iatrogenic side effects of medicines, and enhancing patient quality of life are treatment objectives.

CONCLUSION
This case report emphasize on the importance of recognizing infection in patient with SLE. Clinicians need to be mindful and closely observe patient with severe SLE accompanied with infection to balancing intervention for immunosuppressant therapy and antibiotic.

AUTHOR’S CONTRIBUTION
All of the authors are involved in concepts of the case report. DAAR is contributing in literature search, data acquisition, manuscript preparation and editing, KDKW, IWG and GAPN are contributing as manuscript reviewer.

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