Invasive candida infection as the cause of seizure in a patient with systemic lupus erythematosus: a report of unusual case

Mirza Suryo Adi¹,², Awalia¹,²*

ABSTRACT

Background: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a complication of SLE involving the nervous and psychiatric systems with clinical manifestations including seizures, strokes, myelopathy, neuritis, meningitis, and psychosis. Seizures in NPSLE might be caused by intracranial infection, with bacteria as the most common pathogens. This study reported a rare case of seizure in a SLE patient due to invasive Candida infection.

Case Presentation: A 26-year-old female presented in the emergency department of Dr. Soetomo Hospital Surabaya, Indonesia with seizure, which she has experienced in the last 2 days prior to hospital admission. She experienced a convulsion that lasted 5-10 minutes followed by loss of consciousness. The patient also complained of severe headaches two days before hospital admission. She was diagnosed with SLE in November 2022 and was currently taking methylprednisolone. Physical examination showed Glasgow Coma Scale (GCS) of E3V4M5, fever, dyspnea, and rough rhonchi on the right lung. Chest X-ray indicated pneumonia, while brain computed tomography (CT) suggested subacute to chronic thromboembolism. The patient was diagnosed with NPSLE due to intracranial infection, and hospital-acquired pneumonia (HAP), and was given Levofloxacin. On the 3rd day, a reddish lesion with central healing was found on the cheeks, and the patient had dyspnea, suggesting fungi infection. Methylprednisolone was stopped while fluconazole and urine cultures were initiated. Urine culture suggested Fluconazole-sensitive Candida and consultation with a dermato-venerologist confirmed Candida, thus, Fluconazole was continued along with dexamethasone and Levofloxacin. The patient showed clinical improvement and was discharged after 12 days.

Conclusion: Seizure is one of the most common manifestations of NPSLE, due to intracranial infection. Although rare, we cannot rule out the possibility of fungal infection in NPSLE patients with intracranial infection. Early diagnosis and prompt treatment are critical for better prognosis, as shown in this patient.

Keywords: systemic lupus erythematosus, seizure, infection, invasive candidiasis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease involving multiple body systems, including the nervous system. Genetics, immunological, endocrine and environmental factors have been suggested to play a role in the pathogenesis of the disease.¹ The annual global incidence and prevalence of SLE are estimated to be 0.3-3.15 and 3.2-517.5 cases per 100,000 individuals, respectively. Meanwhile, the annual incidence of SLE in Asia varies from 2.8-8.6 per 100,000 people, while the prevalence ranges from 26.5 to 103 per 100,000 individuals.² The symptoms of SLE might include fever, fatigue, lymphadenopathy, malaise, as well as decreased appetite and weight loss. In addition, the symptoms might also manifest as musculoskeletal, skin and mucosal, renal, lung, cardiac, vessels, ocular, obstetric, endocrine, and hematologic problems, depending on the affected organ system.³

Neuropsychiatric SLE (NPSLE) is a complication of SLE involving the nervous and psychiatric systems with a prevalence of 56.3%, in which 50-60% occur in the first year after SLE onset. Clinical manifestations may vary, such as seizures, strokes, myelopathy, neuritis, meningitis, to psychosis.⁴ Seizure – defined as a transient occurrence of sensory, motor, or autonomic signs and/or symptoms resulted from abnormal excessive neuronal activity in the brain – is considered as a severe and most ominous neuropsychiatric manifestations in SLE and it also caused by several diseases including COVID-19.⁵ The prevalence of seizure among SLE patient is about 2-8%, with young females (22.9-36.5 years old) have higher incidence. Tonic-clonic is the most common seizure presentation (60-88%), followed by seizure with loss of consciousness and seizure with retained consciousness.⁶ The incidence of NPSLE at Dr. Soetomo General Hospital, Surabaya, Indonesia was reported to be 8%, in which majority of the patients were women on their productive age. The most common clinical manifestation found were seizure, headache, cerebrovascular diseases and acute confusion.⁷,⁸

Diagnosis of NPSLE is established based on the presence of neuropsychiatric...
symptoms while excluding other non-NPSLE causes.\textsuperscript{4} In addition, antibody and anti-nuclear antibody (ANA) examination might also be helpful, in which increased of cardiolipin antibody and mixed homogenous nuclear and cytoplasmic speckled ANA pattern with bead confirmation in the positive anti-dsDNA compartment, positive anti-nucleosome, anti-histone, and AMA-M2 from ANA profile are suggestive of NPSLE.\textsuperscript{8}

Infections are a leading complication and cause of mortality in SLE patients. A study by Ghafirah showed that the mortality incidence of SLE patients at Soetomo General Hospital, Surabaya, Indonesia reached 22.2%, with infection as the leading cause.\textsuperscript{10} In addition to disease as an intrinsic factor, SLE treatment involving glucocorticoids or immunosuppressants leads to impaired immune system, resulting in higher risk of infections.\textsuperscript{3,11} Bacteria is the most common pathogens found in patients with SLE, followed by viruses and fungi. Invasive fungal infections (IFIs) are severe complications and leading cause of death in immunocompromised individuals including SLE patients. The most common pathogens that cause IFIs in humans are \textit{Candida} spp., \textit{Aspergillus} spp., and \textit{Cryptococcus} spp.\textsuperscript{11,12} Despite increased use of sensitive diagnostic modalities, identification of IFIs in NPSLE is challenging due to limited number of cases. We herein report a rare case of a 26-year-old female with SLE who presented with seizure due to suspect invasive Candida infection.

**CASE PRESENTATION**

A 26-year-old female presented in the emergency department of Dr. Soetomo Hospital Surabaya, Indonesia on 23 December 2022 with seizure, which she has experienced in the last 2 days prior to hospital admission. She experienced a convulsion that lasted 5-10 minutes followed by loss of consciousness. The patient also complained of a severe headache two days before hospital admission. Fever, hair loss, and decrease of micturition were also reported. No coughing, dyspnea, nausea/vomiting, or defecation problems were reported.

The patient was diagnosed with SLE in November 2022 after experiencing lengthening menstruation and bleeding gums, which led to thrombocytopenia. The patient had a history of anemia for the last 10 years, and had been treated with blood transfusion as well as methylprednisolone. The patient’s ANA test was >400, thus she was treated with methylprednisolone 4 mg daily (sometimes adjusted to 8 mg daily). No history of hypertension, diabetes, or hepatitis was reported. The patient also denied consuming herbs or out-of-prescription drugs. No family history of SLE. She is married with one child, and used to run an online business. She admitted to having been under stress since October 2022.

On clinical examination, the patient looked weak in general, with a Glasgow Coma Scale (GCS) of E3V4M5. Vital signs showed blood pressure of 138/88 mmHg (on nicardipine 0.5 mcg/kg body weight/minute), pulse of 133 beats/minute, respiratory rate of 27 times/minute, and axilla temperature of 38°C. Anemic conjunctiva, dyspnea, and moon face were observed during the head and neck examination, with no jaundice, cyanosis, or lymph gland enlargement. Chest examination showed symmetry with retractions. Auscultation revealed regular single S1 and S2 heart sounds with no gallops or murmur, vesicular breathing on both lungs, and rough rhonchi on the right lung. Abdominal examination indicated normal bowel sounds, convex abdomen, soft to touch, no tenderness and non-
palpable liver and spleen. All extremities were warm, dry, pale, with pitting oedema on bilateral inferior extremities. Neurological examination showed negative neck stiffness. Musculoskeletal examination showed muscle strength of +1/+1/+1+1, no pathological reflexes, no affected joints, morning stiffness, pain on movement, swelling, subcutis nodules, deformities, or subluxations. Urine output was 1550 ml/24 hours, with total input of 2847 ml/24 hours, resulting in a balance of +697 ml/24 hours.

Laboratory examination on December 23, 2022 showed normal hemoglobin, hematocrit, and leucocyte with decreased platelets (127,000/µL), increased random blood glucose (356 mg/dL), normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, slight decrease of albumin (3.17 gr/dL), and increased blood urea nitrogen (31.7). Blood gas analysis showed slight increase of pH (7.53), increased pO2 (189), and slight decrease of paCO2 (34). Urine analysis showed no signs of urinary tract infection but ACR > 300, corresponding to microalbuminuria as usually found in individuals with SLE. On the same day, the chest X-ray showed infiltrate in bilateral supra-perihilar and enlarged heart (Figure 1). Non contrast brain CT (23/12/2023) suggested subacute to chronic thromboembolism at cortical and subcortical of bilateral fronto-parieto-occipital, corresponding to middle cerebral artery (MCA) and posterior cerebral artery (PCA) territories (Figure 2).

The patient was consulted to the neurologist and was diagnosed with loss of consciousness with no meningeal signs, accompanied by neurological deficits in the form of tonic seizure episode, left lateralization, and positive Babinski on the left side. This condition was caused by acute seizure due to suspected metabolic encephalopathy; however, intracranial lesions could not be ruled out. Brain CT with contrast was planned for further investigation.

From history taking, physical examination and supportive examinations, the patient was diagnosed with loss of consciousness with acute symptomatic seizure (suspected NPSLE with differential diagnosis of cardiovascular events (CVA) and intracranial infection), SLE flare-up (SLEDAI score of 28), suspect hospital-acquired pneumonia (HAP), differential diagnostic lupus pneumonitis, steroid-induced hyperglycemia, stage II hypertension Indonesian Society of Hypertension (INASH) 2019 with hypertensive heart disease (HHD), thrombocytopenia, exogenous Cushing syndrome, hypoalbuminemia and dyslipidemia. The patient was treated with 6x200 cc entrosole diet, triofusin 500: KaeEnMg3 1:1 infusion, insulin pump, levofloxacin 1x750 mg, nicardipine pump drip, metoclopramide and 3x100 mg phenytoin intravenously (IV), folic acid (3x1) and potassium chloride syrup (3x 15 ml).

On the third day (25/12/22), a reddish lesion with central healing was found on the cheeks, and the patient had dyspnea. Physical examination showed increased blood pressure to 140/70 mmHg (on nicardipine), pulse (130 beats/min), respiratory rate (28 times/min) with 8 lpm oxygen. Methylprednisolone injection initiated, and 3x2.5 mg dexamethasone was stopped, Fluconazole 200 mg IV was given, ketorolac 3x20 mg, salbutamol 3x1 nebule.

On the fifth day (27/12/22), there was improvement in consciousness with GCS E4V5M6 (fully alert), the patient could talk and had adequate contact. She complained of being unable to move and had breathing difficulty. Urine culture suggested Fluconazole-sensitive Candida; thus, the Fluconazole, dexamethasone, and Levofloxacin treatment was continued.

On the eighth day (30/12/22) the patient complained of white papules on her face, neck, and breast folds. She no longer had fever, both of her arms could be moved, and both legs could be shifted. Consultation with a dermato-venerologist confirmed Candida.

On the 12th day (3/123) the patient reported no seizure or headache, all four extremities could be moved although she was not able to stand yet. The patient was discharged from the hospital on January 4th 2023, a few days after showing stable condition.

On the first follow-up at the outpatient clinic (12/1/23), the patient complained of headaches for 4 days prior to hospital visit, with less intensity compared to previously (before hospitalization), along with hair loss. No complaints of rash, papules on the face, mouth ulcer, fever, dyspnea, cough, or bleeding. She could already stand on her own but still needed assistance to walk. On physical examination, blood pressure was 150/90 mmHg, pulse 97 beats/min (regular), and respiratory rate 20 times/minute. Anemic conjunctiva, moon face, mild pitting edema on both inferior extremities and multiple purpuras were found on physical exam. Motoric strength was +5/+5/+3/+3 with no pathological reflexes. Based on history taking and physical examination the patient was diagnosed with SLE with history of hematologic involvement and neuropsychiatric involvement suspect of intracranial infection; history of HAP suspect lupus pneumonitis; stage I hypertension with HHD, exogenous Cushining syndrome, and dyslipidemia. The patient was treated with 2x360 mg mycophenolate sodium, oral methylprednisolone (16-8-0 to 8-0-0 to 4-0-0), 1x200 mg HCQ, 3x100 mg phenytoin, 1x10 mg lisonipril, 1x1 folic acid, 1x1 calcium lactate tablet and was referred to physical medicine and rehabilitation department.

DISCUSSION

We reported a 26-year-old female presented in the emergency department of Dr. Soetomo Hospital Surabaya, Indonesia with seizure, which she has experienced in the last 2 days prior to hospital admission. She experienced a convulsion that lasted 5-10 minutes followed by loss of consciousness. In addition, she also experienced headaches and hair loss prior to hospital admission. The patient had been diagnosed with SLE and was currently under treatment. The patient was then suspected to have NPSLE with infection.

NPSLE refers to a set of neurological and psychiatric symptoms that are directly related to SLE. The neuropsychiatric signs include but are not limited to headaches, mood disorders, cognitive problems, and seizures. The global prevalence of NPSLE is 56.3%, most occurring within the first year of SLE onset. This is corresponding to the reported case, in which the patient...
presented with seizures and headaches, within the first year after being diagnosed with SLE.

A previous study conducted at Dr. Soetomo General Hospital, Surabaya, Indonesia showed that majority of patients with NPSLE were women on their productive age (15-44 year) with seizure, headache, cerebrovascular diseases and acute confusion as the most common clinical manifestations.7,8 The patient reported in this case also shared similar characteristics: a woman on a productive age (26 years old) presented with seizure and headache. The mechanism of nerve destruction in NPSLE remains unclear, however, almost half of the seizure in SLE patients are associated with metabolic problems or infection.13

Infection is one of the most common complications and is the second most common cause of mortality in SLE patients. Most infections found in SLE patients at Dr. Soetomo General Hospital were pneumonia (70.65%), urinary tract infections (51.09%), and sepsis (35.87%), while cerebral infection was quite rare (5.43%). Another study at Dr. Soetomo General Hospital showed that from 176 SLE patients, 39 were dead (22.2%), with the leading cause being respiratory failure (33.3%) and septic shock (28.2%), both were due to infection, emphasizing infection as the leading cause of mortality in SLE patient. The disease itself, and the treatment (methylprednisolone and immunosuppressive medications) are factors contributing to increased risk of infection among SLE patients.3,10-11 From physical and supportive examination, this patient was first diagnosed with cerebral infection and pneumonia, as rough rhonchi were found in both lungs and chest X-ray showed infiltrate in both lungs. However, on the third day of hospitalization, the patient showed signs of fungal infection instead of bacterial infection, therefore anti-fungal was initiated.

Fungi are the less common cause of infection in SLE patients, coming only third after bacteria and virus, therefore fungi infection in this patient was not predicted at the beginning. Although the prevalence of IFI in SLE patients is quite small (0.64-1.04 %), the prognosis is poor, with above 50% mortality rate. Lungs are the most common organ affected by IFI, and more than 50% of IFI occur in the first three years after being diagnosed with SLE.12,13 As fungal infection is rare, the patient was initially suspected to have bacterial infection. However, the signs found in this patient (pneumonia) correspond to lung infections that are common in IFI. Only after dermatology signs presented on the third day IFI was suspected in this patient.

The most common pathogen that caused IFI was Candida spp. (52.8%), Cryptococcus spp. (18.2%), and Aspergillus spp. (18.2%).14 Invasive candidiasis is often found in immunocompromised patients and has a high mortality rate.15 IFI usually does not give a distinct clinical manifestation, except the specific lesion found in ocular candidiasis and chronic disseminated candidiasis (CDC), although a high fever (up to 42°C) might be found in invasive candidiasis.14,16 The gold standard of invasive candidiasis is culture examination or histopathologic examination of the usually sterile area. However, this examination takes too long (72-96 hours), resulting in postponed diagnosis and treatment, which increases mortality risk. Moreover, this method also had low sensitivity, thus, non-culture and non-histopathological methods of diagnosis are developed by detecting serum Candida antigen and antibody as well as detection of Candida metabolites.18 In immunocompromised patients, Candida can also be found in samples from the respiratory tract (sputum) and the urinary tract (urine).15 About 46-68% patients with candidemia (Candida in blood serum) also had candiduria (Candida in urine).17 This is in line with the reported case, as Fluconazole-sensitive Candida was found in urinalysis conducted on the 5th day of hospitalization.

On the third day a reddish lesion with central healing was found on the cheeks, and the patient had dyspnea, suggesting fungi infection, thus, Fluconazole was initiated. As urine culture on the 5th day suggested Fluconazole-sensitive Candida; and consultation with a dermatovenerologist on the 8th day confirmed Candida, the patient was then diagnosed with NPSLE due to intracranial infection due to suspected invasive candidiasis. Early diagnosis and prompt treatment are pivotal for a good outcome in patients with IFI. Systemic antifungal – such as amphotericin B, flucytosine, azole systemic (fluconazole, itraconazole, voriconazole, posaconazole, ravuconazole, and isavuconazole), and echinocandins – is the treatment of choice for invasive candidiasis. Echinocandin has proven to be effective as the first line therapy in 70-75% patients with invasive candidiasis, however, azole is preferable in patients with invasive candidiasis involving central nervous system as it can easily pass the blood-brain barrier.16 Lyposomal AmB, 5 mg/kg body weight/once daily – with or without oral flucytosine – is recommended for the initial treatment of invasive candidiasis. After the patient responds to the initial treatment, 400-800 mg Fluconazole (6-12 mg/kg body weight) daily can be administered.18 Systemic antifungal is administered for at least 14 days after eradication of Candida spp. from blood serum marked with clinical improvements. Moreover, Fluconazole has been suggested as the first-line therapy for invasive candidiasis in low-income countries with low azole resistance.16 In accordance with this, the patient was given 200 mg Fluconazole IV since the third day of hospitalization. With early diagnosis and prompt treatment, the patient showed rapid clinical improvement and was discharged in a good condition after 12 days.

CONCLUSION

NPSLE is one of the manifestations of SLE, in which seizure is one of the symptoms. Infection is the most common cause of seizure and loss of consciousness in NPSLE, with bacteria as the most common pathogens. We presented a rare case of NPSLE due to intracranial infection due to suspected invasive candidiasis. As the culture examination took quite a long time, establishing the diagnosis of invasive candidiasis became challenging. Treatment with Fluconazole was initiated early in this patient based on the physical examination while waiting for the culture results. In a country like Indonesia where bacteria are more common as the causal of intracranial infection, we could not rule out the possibility of fungal infection,
particularly in immunocompromised individuals such as SLE patients. Early diagnosis and prompt treatment are pivotal in NPSLE due to infection as they will lead to good prognosis, as shown in this patient.

PATIENT CONSENT
The patient had agreed and signed informed consent regarding publishing this clinical case in an academic journal without exposing the patient's identity.

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DISCLOSURE OF CONFLICTS OF INTEREST
The authors declare no conflict of interest regarding the manuscript.

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