DIAGNOSTIC AND MANAGEMENT PROBLEMS IN PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND ANTI N-METHYL-D-ASPARTATE RECEPTOR (NMDAR) ENCEPHALITIS

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ABSTRACT Systemic Lupus Erythematosus (SLE) is a chronic multisystem inflammatory autoimmune disease with unknown aetiology and broad clinical spectrum presentation. In several cases, there is cross-reaction between anti-DNA antibody and ¬N-methyl-D-Aspartate Receptor (NMDAR) subunit 2 (NR2) that can be implicated to multiple brain disorders including stroke, chronic neurodegeneration, epilepsy, and schizophrenia. SLE with anti-NMDAR encephalitis are rare cases, and there was difficulty in establishing the diagnosis and providing therapy because of symptoms and signs in patients who are not specific, and there is no established therapeutic protocol for this disease. A 15-year-old female with encephalitis caused by neuropsychiatric SLE and anti-NMDAR which was successfully treated with high-dose steroid followed by administration of cyclophosphamide and rituximab.

KEYWORDS SLE, Encephalitis, Anti-NMDAR

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic multisystem inflammatory autoimmune disease with unknown aetiology and broad clinical spectrum presentation. SLE is characterized by a loss of tolerance to nuclear antigens, the formation of autoantibodies, and immune complexes that produce complement activation, cell destruction and tissue inflammation. The involvement of the nervous system in SLE patient can lead to neuropsychiatric (NPSLE) symptoms. In several cases, there is cross-reaction between anti-DNA antibody and ¬N-methyl-D-Aspartate Receptor (NMDAR) subunit 2 (NR2) that can be implicated to multiple brain disorders including stroke, chronic neurodegeneration, epilepsy, and schizophrenia. The frequency of anti-NR2 positively in SLE patient is about 30%. NMDAR is ligand-gated ion channels for synapsis transmission and plasticity central nervous system. There was a similarity in sign and symptom between NPSLE and anti-NMDAR encephalitis, and there was no standard therapy for anti-NMDAR encephalitis. This case report showed diagnostic and management problem patient SLE with anti-NMDAR encephalitis.

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Case report

A 15-years-old young female patient was referred from a private hospital and was hospitalized in the intensive care unit because of unconsiousness. Her parents said she complained of headache, agitated and repetitive for asking something for two days before falling to unconsciousness condition. She also complained tonic-clonic seizure in the right arm, tic in left corner lips and low-grade fever. The patient was intubated and admitted to the intensive care unit. The patient was taken ribavirin, phenytoin, dexamethasone, and intravenous immunoglobulin from a private hospital because of suspected meningitis caused by a viral infection.

On physical examination, the patient was coma with normal blood pressure (110/70 mmHg) and slightly high axilla

temperature (37,50C). There was leukocytosis (15,37x103 μ/L) with lymphopenia (5.4% with absolute count was 0.83) incomplete blood count and normal result for procalcitonin serum level, liver function test, renal function test, electrolyte serum and blood gas analysis. Head MRI was in the normal result and from the chest x-ray was shown atelectasis in lung dextra with bilateral bronchopneumonia pattern. Cerebrospinal fluid (CSF) analysis with total protein 30.47 mg/dL, total cell count 94 cell/mL with mono dominant (95%) and no growth from CSF culture.

Viral marker showed non-reactive result for IgM and IgG anti-HSV 1 and 2, IgM and IgG anti CMV, anti-dengue NS1, and also anti-HIV. ANA (IF) test shown speckle pattern with titre 1:1000, ANA profile antigen RNP/Sm (+), SS-A native (60 kDa) (SSA) (+), Ro-52 recombinant (52) (++), AMA-M2 (M2) (+). In third days hospitalization, there was increasing in procalcitonin serum level (6.83 ng/mL). The patient was examined IGRA with negative result, normal flora (staphylococcus, coagulase-negative) from sputum gram culture and no growth from blood and urine culture. Patient also experienced electrolyte disturbances during hospitalization with hypopotassemia (2,6 mmol/L), hypocalcemia (8,4 mg/dL) and hypomagnesemia (0,8 mg/dL).

Based on laboratory and another supported data result, the patient was diagnosed with a decrease of consciousness because of suspected NPSLE differential diagnose with tuberculosis meningitis, accompanied by ventilatory associated pneumonia and electrolyte imbalance. The patient was taken intensive phase antituberculosis drug (300 mg isoniazid, 450 mg rifampicin, 150 mg pyrazinamide, 750 mg ethambutol) and also antibiotic meropenem 2 gr intravenous every 12 hours, amikacin 1000 mg intravenous every 24 hours for pneumonia treatment and pulse dose methylprednisolone (1000 mg in 200 mL NaCl 0,9%) for three days and continued with cyclophosphamide intravenous (1000 mg in 100 mL NaCl 0,9%) and maintenance therapy for corticosteroid intravenous (62,5 mg intravenous every 12 hours) for NPSLE treatment. The patient also takes plasmapheresis for autoimmune disease therapy and 1 gr calcium gluconate, 50 mEq KCl and 4 gr MgSO4 intravenous drip for hypocalcemia, hipopotasemia and hypomagnesemia.

In 10th day hospitalization, there was no response after taking all of the therapy above. The patient was suspected anti-NMDAR encephalitis because of the similarity sign, and symptom between NPSLE and anti-NMDAR encephalitis and that was supported from abdominal ultrasound result that shown cystic lesion with the solid component inside in left adnexa (3,6 x 3,2 cm) with unclear vascularization. The patient has undergone biopsy surgery of left adnexa with histopathological anatomy examination result shown teratoma ovari. The possibility of anti-NMDAR encephalitis was supported from histopathological anatomi finding. The patient also planned to examine antibody anti-NMDAR from serum and CSF. There was a positive result for serum and CSF antibody anti-NMDAR.

Based on the results of the supporting examination above, the patient was diagnosed with NPSLE, encephalitis anti-NMDAR, tuberculosis meningitis, ventilatory associated pneumonia, and electrolyte imbalance. In 18th-day hospitalization patient take high-dose methylprednisolone intravenous (1000 mg in 200 mL NaCl 0,9%) for five days, followed with rituximab intravenous (1000 mg in 100 mL NaCl 0,9%) for the next day and methylprednisolone maintenance dose (62,5 mg intravenous every 12 hours). Antibiotic such as meropenem, amikacin and also antituberculosis drug was continued.

The patient was fully alert in 30th days hospitalization and moved out from the intensive care unit to another ward. In 41st day, patient take second rituximab drip intravenous (1000 mg in 100 mL NaCl 0,9%) and maintenance corticosteroid (methylprednisolone) was continued. The anti-tuberculosis drug was continued until six-month therapy. On 45th days the patient was policlinic care.

Discussion

This patient was diagnosed with SLE based on American College of Rheumatology (1997 ACR revised criteria) and Systemic Lupus International Collaborating Clinics (2012 SLICC criteria). SLE diagnoses were made if it meets at least 4 of 11 from ACR revised criteria that occur concurrently or with a grace period or found four or more criteria based on SLICC criteria, with at least one clinical criteria and one laboratory criteria. Based on the ACR criteria, there was found symptoms and signs of neurological abnormalities (seizures), haematological abnormalities (lymphopenia), immunological abnormalities (anti-Sm positive), positive Antinuclear antibodies. As for the SLICC criteria, neurological signs and symptoms (seizures, peripheral neuropathy and acute confusional state), lymphopenia, and with positive ANA test results with ANA positive anti-Sm profile.[1]

Anti receptor N-Methyl-D-Aspartate (anti-NMDAR) encephalitis is an autoimmune disease related to a tumor on 60% cases, usually a teratoma ovari or testis tumour.[4,5,6] About 80% of anti-NMDAR encephalitis patients are women with age more than 18 years old.[6] A cross-reaction between antibodies anti-DNA with N-Methyl-D-Aspartate (NMDAR) receptor subunit 2 (NR2) completely. The frequency of anti-NR2 positive around 30% in SLE patients.[3] About 70% of patients with anti-NMDAR encephalitis begin with the prodromal phase for 5-14 days, include fever, weakness, an inability to concentrate, nausea, vomiting, diarrhoea, headache or flu-like syndrome.[4,6-9] Followed with phase psychotic and/or seizure characterize by emotion and attitude disorders, covering apathetic, fear, depression, cognitive decline, psychosis (delusion and hallucinations), ataxia and chorea. Patients often experienced oro-facial dystonia and dyskinesia during this phase.[4,6,9]

The definitive diagnosis of anti-NMDAR is based on the presence of one or more major group symptoms and anti-GluN1 IgG antibodies after exclusion from other abnormalities. The antibody test must include a CSF examination. If only serum is available, confirmation tests must be included (immunohistochemistry of living neurons or tissue in addition to cell-based assay examinations).[10] In this patient was found teratoma ovari from histopathology anatomy biopsy from left adnexa and also positive result antibody anti-NMDAR from serum and CSF. Some treatments are said to improve the outcome. The administration of immunoglobulin combined with methylprednisolone is used as the first line of therapy. As an alternative, it can be said to use plasmapheresis. But if there is no improvement in the condition, then it can be continued with rituximab and cyclophosphamide. Medical therapies for suspected anti-NMDAR encephalitis include initial therapy with acyclovir until the herpes simplex virus (HSV) is excluded. Anti-seizure therapy is needed to control seizures. Patients usually undergo length of stay in intensive care 2-14 months. The recovery period can reach three years, or more and patients typically do not always return to the early level of motor and cognitive function.[4]

In our case, treatment of NPSLE with anti-NMDAR encephalitis for this patient with high-dose steroids (1 gr methylpred-

nisolone) for three days followed by 1 gr cyclophosphamide intravenously one time and continued with maintenance dose steroid therapy (62,5 mg every 12 hours). Additional therapy was given after positive result from antibody anti-NMDAR steroids, there was 1 gr methylprednisolone intravenously for five days, followed by 1 gr rituximab intravenously for two times (one times every two weeks) and continued with maintenance dose steroid therapy. For high dose, intravenous immunoglobulin therapy and antiviral therapy (ribavirin) were given previously at the Private Hospital before being referred to General Hospital and plasma expander one time while being treated at the ICU.

The patient's prognosis depends on the initial diagnose, the proper implementation of immunomodulatory therapy, and in the case of paraneoplastic, completely removing the tumour. By giving aggressive therapy shows a good prognosis. In a cohort of 360 patients, almost 75% showed complete or near-complete recovery.[4,7] About 25% of patients had severe neurologic deficits or death.[7] For our case, the patient had a good prognosis, and patient contact was showed improvement after ten days (day 29th of treatment) from the first rituximab therapy. Patients begin to be able to open her eyes and regain fully alert on the 30th day of treatment.

Conclusion

A 15-year-old female with Systemic Lupus Erythematosus and Anti-NMDAR Encephalitis. Anti-NMDAR encephalitis is autoimmune encephalitis and is often missed in diagnosis. This disease is related to the presence of tumours, especially teratomas. Anti-NMDAR encephalitis can occur simultaneously with SLE due to a cross-reaction between anti-DNA antibodies and NR2. The diagnosis is confirmed by NMDAR antibodies in the serum or CSF of the patient. We were successfully treated NPSLE with anti-NMDAR encephalitis patient with combination high-dose steroid followed by cyclophosphamide, and rituximab therapy.

Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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