



## A Systemic Lupus Erythematosus Accompanied with Myelodysplastic Syndrome, Grave's Disease, and Sub-Acute Subdural Hemorrhage: A Case Report

I Nyoman Suarjana<sup>1\*</sup>, Anggrada K. Utomo<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Ulin General Hospital, Banjarmasin, Indonesia

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#### \*Corresponding author:

I Nyoman Suarjana

#### E-mail address:

[drnyomansuarjana@gmail.com](mailto:drnyomansuarjana@gmail.com)

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### ABSTRACT

**Background:** The systemic lupus erythematosus (SLE) is a disease of autoimmune etiology affecting multiple systems, involving most commonly females of the reproductive age group and different clinical manifestations in each individual. **Case presentation:** A 23-year-old female patient with systemic lupus erythematosus (SLE) presented with myelodysplastic syndrome (MDS), Grave's disease, and sub-acute subdural hemorrhage (SDH). She had chief complaints of severe headache and gum bleeding. Three weeks earlier, the patient experienced a head injury. SLE was diagnosed on biological and immunological clinical ACR criteria and the patient never had a therapy before. Bone marrow aspiration (BMA) test was performed with MDS result. Thyroid function test was performed with the result of decreased Thyroid Stimulating Hormone (TSH) and increased FT4 with diffused enlargement of thyroid gland. Brain CT Scan resulted in sub-acute SDH with midline shift of 1.13 cm to the left. The patient underwent subdural drainage with local anesthesia and received steroid, azathioprine, thiamazole and non-selective beta-blocker. She was hospitalized for 21 days and was discharged with good condition. **Conclusion:** Further investigation of the patient is needed to fully understand the correlation between MDS, Subdural Hemorrhage and Grave's Disease in associated with SLE.

### 1. Introduction

Systemic lupus erythematosus (SLE) is a disease of autoimmune etiology affecting multiple systems, involving most commonly females of the reproductive age group and different clinical manifestations in each individual. MDS, Graves' disease, and SDH in this patient may be clinical manifestations of SLE. Hematological manifestations of SLE may present in many forms, such as cytopenia and bone marrow dysplasia, and dysplasia is found to be reversible during the course of the disease. Recent studies suggested an increased risk of MDS in patients with autoimmune diseases.<sup>1</sup> SLE has commonly associated

with hypothyroidism related autoimmune. The association between Graves' disease and SLE is rarely described in the literature.<sup>2</sup>

Subdural hemorrhage in this patient is caused by previous head trauma. However, SLE also is involved despite subdural hemorrhage rarity in SLE.<sup>3,4</sup> We report a case of a 23-year-old female with SLE, MDS, Graves' disease, and sub-acute SDH. She was hospitalized for around 21 days in the ward of Ulin General Hospital and underwent subdural drainage.

### 2. Case Presentation

A 23-year-old female patient came to the Ulin

General Hospital of Banjarmasin with a chief complaint of severe headache after falling down 4 days prior to admission and getting worse over time. The pain did not improve by resting or consuming pain relief drugs. She also complained of gum bleeding the day before admission. Three weeks earlier, she said that she was beaten by her brother on her left face, producing extensive bluish bruises. She has felt a lump on her neck for the past 3 years, both eyes seemed to be more protruded and both hands were often trembling. She has lost  $\pm$  5 kg of weight within the past year, had irregular menstruation, and had 2-3 times of defecation each day.

The patient complained about her hair falling out easily and both eyebrows thinned out for the last 3 years and worsened in the past year. Her forehead seemed larger. There were no rashes on her face and her skin was not sensitive to sunlight. She had no joint pain. The patient stated that she often had painless mouth ulcers in the past year. Four months before this admission, she was hospitalized due to low hemoglobin and received 4 packs of packed red cell transfusion and was told that she has low iron levels. She had hyperthyroid for the last 3 years. However, she did not take any medication.

On physical examination, the patient had alopecia, exophthalmos, gum bleeding, bilateral enlargement of the thyroid gland, and resting tremor without lateralization N. Respiratory rate was 18 breaths/minute with clear lung auscultation. The pulse rate was 125 beats/minute, blood pressure was 130/70 mmHg with pain numeric rating scale was 7 on her head.

Hemoglobin level was 11.9 g/dL with mean corpuscular volume and mean corpuscular hemoglobin 58.5 fL and 17.5 pg, respectively. The platelet count was 51.000/ $\mu$ L. TSH level was 0.001 uIU/ml and FT4 level was 25.95 pmol/l. Urinalysis was normal. The anti-nuclear antibody test (ANA) was positive with a speckled pattern and titer > 1: 1000. Bone marrow aspiration revealed Myelodysplastic Syndrome Refractory Anemia (MDS-RA). Brain CT scan revealed subdural hematoma at right temporal-

parietal with midline shift to the left 1.13 cm. The electrocardiogram showed sinus tachycardia. Thyroid USG showed consideration of Graves' disease.

Subdural drainage was performed by a neurosurgeon with local anesthesia. After the surgery, she received antibiotics and intravenous analgesics. She received azathioprine and methylprednisolone as SLE therapy, thyrozol, and propranolol for Graves' disease, and ferrous sulfate for iron deficiency anemia. After 7 days of postoperative care, she was discharged. She had visited the rheumatology clinic three times for follow-up. Laboratory reexamination was performed during follow-up with normal results on hemoglobin, leukocytes, and platelet, whereas the blood smear showed normal erythrocytes, leukocytes, and platelet count and morphology. TSH level was 0.668 uIU/ml and the FT4 level was 10.52 pmol/l.

### 3. Discussion

Systemic lupus erythematosus is an autoimmune condition with a variety of clinical features in which immune complexes cause tissue injury involving multiple organs and systems.<sup>5</sup> The manifestations of SLE are associated with various autoantibodies, the formation of an immune complex, and several immune processes.<sup>6</sup> The diagnoses of SLE is usually made clinically, at least four of the 11 American College of Rheumatology Classification criteria; malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis (pleural effusion, pericardial effusion), renal disorder, neurological disorder, hematological disorder, immunologic disorder and antinuclear antibodies.<sup>7</sup> The SLICC concern that SLE is an autoantibody disease with a presence of at least one immunologic criterion, and for classification a histologically proven nephritis that compatible with SLE, if ANAs (Antinuclear Antibodies) and dsDNA (antibodies to double-stranded DNA) were present. However, the SLICC has a lower specificity than the 1997 ACR criteria.<sup>8</sup> Our patient fulfilled the above criteria and the diagnosis of SLE was made.

About 60% of SLE cases had a central nervous system involvement.<sup>9</sup> SLE patients that have

neuropsychiatric symptoms are categorized as 'neuropsychiatric lupus' (NPSLE).<sup>10</sup> There are 19 neuropsychiatric syndromes, based on The American College of Rheumatology, that may appear with SLE, such as focal manifestations (e.g., stroke or seizure) and more complex syndromes (e.g., depression, anxiety, memory deficits, and a decline of cognitive function).<sup>11</sup>

In the pathogenesis of cardiovascular disease in SLE patients, primary and secondary causes have been suggested. The primary causes include vasculitis, specific anti-neuronal antibodies, and lupus anticoagulant. As secondary causes, renal disorders, hypertension, and steroid administration have been suggested.<sup>12</sup>

Cerebral vasculitis in SLE is a relatively rare SLE case, and the underlying mechanisms are not fully understood. It is suggested that the mechanisms involved include autoantibody-mediated activation of the thrombotic system, vascular damage associated with the immune complex, and autoantibodies that directly damage CNS, including anti neuronal, anti-ribosomal P, and anti lymphocytotoxic antibodies.<sup>14,15</sup> There are 0.4-7% of SLE cases with Cerebral hemorrhage and it is usually caused by inherent or iatrogenic factors (e.g., arterial hypertension, thrombocytopenia, or anticoagulation).<sup>16</sup> The most commonly occurring cerebral hemorrhage in SLE is subarachnoid hemorrhage, followed by intracerebral hemorrhage. Meanwhile, epidural and subdural hemorrhage is very rarely found in SLE.<sup>17</sup>

Subdural hemorrhage frequently occurs due to injury at cerebral bridging veins secondary to head trauma.<sup>18</sup> Subdural hemorrhage generally begins to be symptomatic within 72 h and usually occur in young adults. A spontaneous subdural hemorrhage is an unusual event, but it is a serious condition. The reported incidences of spontaneous subdural hemorrhage relative to total subdural hemorrhage have ranged from 2 to 6.7%.<sup>19</sup>

In an autopsy material of 57 patients with SLE, Ellis and Verity found two cases with subdural hematoma out of a total of 24 cases with CNS

hemorrhages. CNS vasculitis was found in many patients with subarachnoid hemorrhage, but not in the cases with subdural hematoma.<sup>20</sup>

In this case, subdural hemorrhage was preceded by trauma. However, subdural hemorrhage can also be caused by thrombocytopenia in SLE. In order to establish the diagnosis of subdural hemorrhage due to SLE, a biopsy is needed.

Ten to twenty percent of Myelodysplastic Syndrome can occur simultaneously with autoimmune disease, including SLE, which can be a challenge to identify.<sup>21</sup> In a retrospective study of 2471 patients, MDS was found after autoimmune disorder, one of which is SLE.<sup>22</sup> Other than that, the use of drugs for SLE such as Azathioprine can also increase the risk of MDS.<sup>23</sup> There is also dysplasia of the erythroid lineage that has been reported with SLE patients.<sup>24</sup> Recently, Voulgarelis et al reported a bone marrow histological findings in SLE which are a variety of histological findings including bone marrow necrosis, stromal alterations, hypocellularity, dyspoiesis, and distortion of normal bone marrow architecture.<sup>25</sup>

True MDS in SLE patients was unlikely, this is caused by 1) cytopenia that resolved with the SLE medication only; 2) there were no abnormal karyotypes found in SLE patients; 3) No SLE patients developed refractory anemia with excess blasts; and, most importantly, 4) a resolved of bone marrow dysplasia SLE undergoing remission.<sup>16</sup> This patient had never received therapy for SLE. After receiving SLE therapy for 3 months, blood count and blood smear examination revealed normal results. Reexamination of bone marrow aspiration should be performed to confirm that the bone marrow dysplasia disappeared with SLE's treatment.

Graves' disease is a thyroid autoimmune disease, with typical circulating autoantibodies that can activate the thyroid hormone receptors. Thus causing hyperthyroidism, goiter, and ophthalmopathy.

Confirmation of the Graves' disease diagnosis can be ruled with Biomolecular tests such as TRAb (Thyroid Stimulating Hormone Receptor Antibodies) or TSI (Thyroid-Stimulating Immunoglobulin). This

procedure is relatively cost-effective. The study of thyroidal blood flow with ultrasonography may be useful for the diagnosis of Graves's disease.<sup>17</sup>

SLE can affect multiple organs of the human body and is characterized by autoantibodies formation. Previous studies have reported that thyroid autoimmune disease and rheumatic disorders can present in an unusual relationship.<sup>18</sup> According to the previous study, the presence of hypothyroidism in SLE patients is quite high than in the general population.<sup>19</sup>

However, another previous study revealed that there is a considerable variation in the prevalence of Graves' disease in SLE. Two case-control studies found a higher prevalence of hyperthyroidism in SLE patients.<sup>20</sup> Other studies report no such increase in the prevalence of hyperthyroidism in SLE patients.<sup>21</sup> A study on the Korean population in 2017 found that patients with SLE accompanied with thyroid autoimmune disease were higher than in the previous study, especially Graves's disease and Hashimoto's thyroiditis with 0.94% and 2.68% cases respectively.<sup>22</sup>

The association between SLE and thyroid disease can be caused by a loss of immunological tolerance and also caused by the exaggeration of both cellular and humoral immune responses. The autoreactivity of T cells and B cells especially in SLE can also damage the thyroid gland and induce AITD.<sup>23</sup> This patient should receive TRAb or RAIU test to confirm Graves' disease diagnosis. Afterward, TSH and FT4 should be monitored frequently to assess thyroid function following treatment.

#### 4. Conclusion

European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) has developed new classification criteria for SLE, to fully filled this criterion, this patient should be tested for anti-dsDNA or C3/C4. We need to investigate further the cause of subdural hemorrhage, and whether there was a relationship with SLE or not. The diagnosis of MDS requires a cytogenetic examination that had not been performed on this patient. Reexamination of bone

marrow aspiration should be performed to confirm that the bone marrow dysplasia will be disappeared with SLE's treatment. While TRAb or RAIU test should be done to confirm Grave's disease diagnosis. We need further investigate the cause of subdural hemorrhage, and whether there was a relationship with SLE or not.

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